Neuron, Vol. 43, 165–168, July 22, 2004, Copyright ©2004 by Cell Press

Problems and Solutions for Circuits and Synapses in Parkinson's Disease

Meeting Report

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Introduction

The following is a synopsis of the discussions and conclusions from the meeting "Neuronal Degeneration and Novel Therapeutic Approaches in Parkinson's Disease" that was convened at the Juan March Center for International Meetings on Biology Workshops in Madrid. The organizers were C.W. Olanow (Mt. Sinai Medical Center, NY), Jose A. Obeso (University of Navarra, Pamplona), and Rosario Moratalla (Instituto Cajal, Madrid). The organizers and the Instituto Juan March brought together a strong group of clinicians and basic scientists, and in doing so, they hosted a scientifically as well as medically relevant state-of-the-art workshop on brain systems function and new therapeutic strategies that are relevant to Parkinson's disease. In addition to providing a review of some of the specific discussions and presentations from the meeting (due to space restrictions, it is not possible to review all of the presentations), this report is intended to serve the general reader with an overview of this rapidly developing field.

Without pharmacological treatment, a typical person afflicted with Parkinson's disease displays a stiff posture and slightly unstable gait, with trembling hands and arms, and moves laboriously with short steps. The lack of movement control, tremors, instability in their posture, gait disturbance, masked face, muscle rigidity, vocal diminution, or additional autonomic reactions are physically as well as emotionally incapacitating, and many patients with Parkinson's disease experience emotional difficulties in dealing with the disease, although their cognitive functions are largely unaffected. This surprising range of symptoms is caused by the relatively selective loss of a small population of approximately 500,000 dopaminergic neurons in the brain. These cells are situated deep in the midbrain in a region called the substantia nigra (literally meaning "black substance") whose distinctive coloration is caused by melanin produced by the neurons in this region. It is the case that in the aging brain some of these dopaminergic neurons will stop functioning properly over time; yet, the normally aging brain somehow manages to compensate for the loss of about 70%–80% of these cells or their synapses over time. It is only when a very small number of functional dopaminergic synapses remain that the symptoms of Parkinson's disease appear.

The use of L-dopa as a therapy for the treatment of Parkinson's disease has been hailed as one of the most successful examples of drug therapies for the treatment of any neurological disease. When first introduced, the pharmacological substitution therapy provided by L-dopa revolutionized the treatment of Parkinson's disease (Tolosa et al., 1998). The alternative neurosurgical treatment (pallidotomy) that was available prior to the introduction of L-dopa in the 1950s was largely abandoned, since it was anticipated that L-dopa was a sufficient treatment for Parkinson's disease. Moreover, it was hoped that this type of pharmacological substitution would be possible for many other neurodegenerative diseases.

As it turned out, the situation wasn't quite so simple. While L-dopa is a remarkably effective treatment, after 5 to 10 or 15 years of treatment, L-dopa becomes less effective in a manner that is quite distinct from typical drug-induced tolerance. For instance, patients experience severe fluctuations in the drug effect. The so-called "OFF" phenomenon describes the time when the drug somehow becomes ineffective for the patient. At such times, the patient freezes up momentarily and loses mobility. The "ON" times are when the drug works and the patient gains mobility. However, both the ON and OFF times may be unfavorable. Symptoms can fluctuate wildly with L-dopa treatment or analog drugs, in effect resulting in problems during both the ON and OFF times. During OFF times, freezing, rigidity, and an inability to initiate movement is further compounded by side effects during ON times, such as involuntary movements generated by the drug. These hyperactive movements and dystonia (abnormal muscle tension and postures) are very debilitating. Since the ON-OFF phenomena in Parkinson's disease are so debilitating, some neurosurgeons and neurologists have returned to brain surgery as a means to restrain these symptoms. Likewise, deep-brain electrical stimulation (DBS) of the subthalamic nucleus has also been shown to alleviate some of the movement disorders of Parkinson's disease (Benabid, 2003; Lozano et al., 2002; Welter et al., 2004).

What accounts for the loss of the effectiveness of L-dopa therapy and what are the neurobiological mechanisms that underlie the ON-OFF phenomena? It is reasonable to assume that one of the reasons L-dopa becomes less effective is that it cannot be taken up by the depleted number of surviving dopaminergic neurons. If indeed these side effects associated with prolonged L-dopa therapy reflect a loss of these dopaminergic neurons and their connections and not just the loss of dopamine, then the design of new therapeutics may need to deal with more than just the replacement of a single substance, dopamine, and rather we are left with the more complex issue of trying to recreate synaptic networks and/or preserve them from degeneration (Isacson et al., 2003).

The Physiological State of Neuronal Circuitry that Contributes to the Signs and Symptoms of Parkinson's Disease

In order to understand the causes of Parkinson's disease and develop effective alternative therapies for the disease, it will ultimately be critical to understand the

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neural circuitry affected by the disease. The abnormal function of the neuronal connections that generates Parkinsonism is typically described as being centered within the basal ganglia regions of the brain. Loss of dopaminergic neurons in the substantia nigra and ultimately a decline in dopamine levels result in abnormal striatal neuronal physiology, which is followed by dysfunction in the pallidal nuclei. Dr. Peter Strick (Departments of Neurobiology, Psychiatry, and Neurological Surgery, University of Pittsburgh, PA) discussed which cortical areas are the targets of these basal ganglia outputs and showed that the functionally segregated circuits that arise from the basal ganglia also have a surprising degree of topographic organization in the cerebral cortex (Middleton and Strick, 2002). These experiments indicate that there may be a widespread effect of basal ganglia in the processes that would underlie some of the pre- or nonmotor effects that are seen in Parkinson's disease as well as Huntington's disease.

In keeping with this theme of complexity and wide reach of the basal ganglia system, there is also evidence that ventral putamen may also participate in a circuit that receives input from the amygdala and that this pathway would then provide the limbic system with access to the motor cortex. This slightly broader view of basal ganglia function was also the message put forward by Dr. Yves Agid (Hopital de la Salpetriere, INSERM U289, Paris, France), who presented evidence suggesting a role for basal ganglia in obsessive-compulsive disorders (Houeto et al., 2002). The implication of these studies is that, in various contexts, the classic limbic circuits also have access to pallidum, the subthalamic nucleus, substantia nigra, and thalamus. Dr. Ann M. Graybiel (Massachusetts Institute of Technology, Cambridge, MA) presented work examining the hypothesis that the brain systems that include striatum are involved in adaptive mechanisms used to adjust cerebral cortical activity to various behaviors, including motor and action plans. Using multiple electrode recordings, Graybiel and colleagues demonstrated that the normal function of the cortical striatal and associated thalamocortical systems as well as other corticofugal systems can be finely tuned based on prior actions and movements executed through this circuitry (Courtemanche et al., 2003). While none of these speakers addressed the particular dopaminergic abnormalities seen in Parkinson's disease, the themes that they highlighted concerning the role of basal ganglia in premotor and motor control are very likely to be important for understanding the mechanisms underlying the motor control symptoms seen in Parkinson's patients, as abnormalities of these basal ganglia circuits are thought to underlie both the motor control deficits in patients with the disease and the drug-induced side effects. The various hypotheses for how abnormal activation of the basal ganglia leads to tremor and rigidity are perhaps best explained by the work of Alexander et al. (1990), who demonstrated an abnormal synchronization of pallidal neuronal discharge due to the loss of dopamine in the system. Finally, to account for the role of the basal ganglia in both motor execution and motor learning, Susan Haber has suggested a model involving an integrated network of connections betwen the basal ganglia and frontal cortex that controls goal-directed motor behavior. Reciprocal and nonreciprocal connections between the striatonigral and thalamocortical networks allow for feedforward and feedback transfer of information (Haber, 2003). When these circuits go awry—with the loss of dopamine and synaptic control in putamen in Parkinson's disease, the increased firing rate of the globus pallidus, and the similarly overactive subthalamic nucleus—surgical intervention can be an effective treatment option (Welter et al., 2004). Indeed, such surgery prevents the dopamine loss-induced feedback inhibition of initiation of movement seen in Parkinson's disease. However, some dopamine function is still required for such surgical interventions to be effective, and the primary desired effect in patients is to remove their drug-induced side effect through the basal ganglia loops.

Synaptic Interactions and the Role of Dopamine Receptors in the Function and Dysfunction of the Dopamine System

Dr. Rosario Moratalla described the roles of dopamine D1 and D2 receptor subtypes in L-dopa-induced dyskinesia models of Parkinson's disease. D1 receptor knockout mice have reduced dyskinesia. This contrasts with knockout mice lacking D2 receptors, which show an elevation of some dyskinesias after L-dopa inducement (Centonze et al., 2003a, 2003b; Xu et al., 1994). The implication of these studies is that a functional balance of dopamine D1/D2 receptors is required for the normal maintenance and function of the basal ganglia circuitry involved in the control of movements. Dr. Paolo Calabresi (Department of Neuroscience, University of Rome, Rome, Italy) presented data to suggest a role for striatal synaptic plasticity in L-dopa-induced dyskinesias. High-frequency stimulation of cortical afferents will induce LTP, and in both control rats and L-dopa-treated Parkinsonian rats that did not display dyskinesias, subsequent low-frequency stimulation of these synapses results in depotentiation of the response. This effect is dependent on the D1 class of dopamine receptor. However, in dyskinetic rats, such low-frequency stimulation does not lead to a depotentiation or reversal of the LTP effect. This work suggests that the abnormal synaptic plasticity and the loss of homeostatic control of this circuit may be linked with the development of L-dopa-induced dyskinesias (Picconi et al., 2003). Dr. Christian Gross provided additional insight into how the abnormal circuitry associated with Parkinson's disease affects output (University of Bordeaux, Bordeaux, France). Using the MPTP model of Parkinson's disease, Dr. Gross described presymptomatic and symptomatic shifts in DA function that are similar to those seen in Parkinson's patients. Key components of this shift were increases in dopamine metabolism (as described previously) as well as an upregulation of the dopamine D2 receptor. It was also proposed that the subthalamic nucleus and globus pallidus would also increase their firing rates as a form of compensation for the initial loss of dopamine (Meissner et al., 2003).

What Are the Genetic and Environmental Contributions to Parkinson's Disease and How Can This Pathophysiology Be Corrected?

In recent years, it has become clear that both intrinsic/genetic and extrinsic/environmental factors contribute

to Parkinson's disease. Dr. William Langston (Parkinson's Institute, Sunnyvale, CA) presented data to suggest that environmental factors may affect the symptoms associated with late-onset Parkinson's disease (Tanner et al., 1999). On the other hand, in recent years a number of susceptibility genes and genes related to α synuclein and parkin have been implicated in the pathophysiology of both idiopathic and genetic disease (Farrer et al., 2001, 2004; Tan et al., 2003). Whatever the root, the obvious question that arises is how to halt the pathological progression of the disease. Dr. C. Warren Olanow discussed the role of the ubiquitin proteasome system in the disease. Dr. Olanow presented evidence to show that it is possible to experimentally induce major degeneration in the dopaminergic system by means of protein misfolding. This idea was further elaborated by Dr. Mark Cookson (National Institutes of Health, Bethesda, MD), who showed that overexpression of mutant or normal α synuclein or exposure to proteosome inhibitor can result in selective toxicity of midbrain dopamine neurons (Singleton et al., 2003; Cookson, 2003a, 2003b). Proteosomal dysfunction may in fact be a common component of many neurodegenerative diseases.

Neural Connectivity and Synapse Repair

The final part of the meeting revolved around potential therapies. Andreas Lozano (University of Toronto, Toronto, Canada) presented examples of surgical therapies that have been shown to be effective in treating aspects of the disease (Lozano et al., 2002). Dr. Lozano also presented a review of gene therapy approaches and potential cell transplantation therapeutics that are currently under investigation. The use of fetal mesencephalic dopamine cell transplants has been the focus of much interest and investigation in the field. Functional motor deficits associated with Parkinson's disease can be reduced after fetal dopaminergic cell transfer to the human caudate-putamen. Interestingly, these fetal dopaminergic cells appear to be resistant to the underlying disease process that continues to destroy the patient's own dopaminergic system, even after transplantation (Piccini et al., 1999, 2000). That said, the approach is not without problems and side effects. For instance, a subset of transplanted patients develop dyskinesias after transplantation. It has been proposed that the unregulated release of dopamine from fetal neurons is the cause of unwanted dyskinesias seen in these patients (Freed et al., 2001; Olanow et al., 2003). In addition, despite the apparent successes of the fetal cell transplantation approach, clinical trials aimed at assessing more systematically the therapeutic value of this approach have met with mixed results. Dr. Stanley Fahn (Columbia University, NY), presented a review of the recent double-blind clinical trials using mesencephalic derived cell transplants as a Parkinson's disease therapy (Freed et al., 2001). Dr. Fahn outlined the lessons learned and made recommendations for the design and approach of future studies (Freed et al., 2001; Olanow et al., 2003). Several speakers also argued that, in evaluating the potential of various therapeutic approaches, it will be important to develop better criteria for individual patient selection in clinical trials. Despite these limitations, there are reasons to be optimistic that improved understanding of this system will lead to solutions to these problems. For instance, there is much evidence of inherent brain plasticity, suggesting that it may be possible to design therapies that take advantage of this intrinsic plasticity and may therefore be more effective in the overall treatment of the disease than current drugs.

Finally, several speakers also discussed alternative transplantation approaches, for instance, the transplantation of neural stem cells or embryonic stem cells. Dr. Ole Isacson (Harvard Medical School, Boston, MA) and Dr. Ernest Arenas (Karolinska Institute, Stockholm, Sweden) made the case for stem cell-based cell replacement and neuroprotection strategies as alternatives to fetal dopamine cell transplantation. First, Dr. Arenas described the molecules and pathways that are involved in normal neurogenesis and proliferation of midbrain dopaminergic neurons (Castelo-Branco et al., 2003) and focused specifically on the role of the Wnt family in the regulation of the proliferation of Nurr-1-positive precursors. Insights that come with the understanding of the normal pathways that control dopaminergic development may be useful for designing strategies to generate dopaminergic neurons from other sources, such as ES cells or neuronal stem cell populations. Patrik Brundin (Lund University, Lund, Sweden) reviewed recent evidence in the field suggesting that ES cells may be a reasonable starting point and cell source for generating the midbrain dopamine neurons for future transplantation and could overcome some of the technical and political problems associated with using a mixture of fetal primary neurons. Previous work has shown that mouse dopaminergic neurons can be expanded in a cell culture dish from growth factor expanded E12 ventral mesencephalic precursor cells, as well as from transfected ES and progenitor cell cultures (for examples, see Wagner et al., 1999; Kawasaki et al., 2000; Lee et al., 2000; Chung et al., 2002; Kim et al., 2002; Castelo-Branco et al., 2003). More importantly, undifferentiated ES cells or embryoid bodies can be injected into the brain and can there spontaneously differentiate into neurons (Deacon et al., 1998). Further, naive or predifferentiated ES cells implanted into a dopamine-depleted striatum can develop and function as replicas of the dopaminergic neurons that are lost in Parkinson's disease and can restore amphetamine-induced motor symmetry and cortical activation (Bjorklund et al., 2002; Kim et al., 2002) that are lost in Parkinson's disease.

In conclusion, this meeting highlighted the tremendous progress that has been made in recent years in both our understanding of the pathogenesis of Parkinson's disease and in the development of therapeutics to treat the disease. If there is one theme to be taken away from this meeting, it is that Parkinson's disease is a multisystems disease, affecting a widespread circuitry beyond just the substantia nigra, and efforts aimed at developing novel therapeutic treatments will certainly need to grapple with this complexity. While there are many reasons to be optimistic that better treatments for Parkinson's disease are within sight, it is also clear that many challenges still remain.

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