TECHVIEW: IMAGING

A Molecular Map for Neurodegeneration

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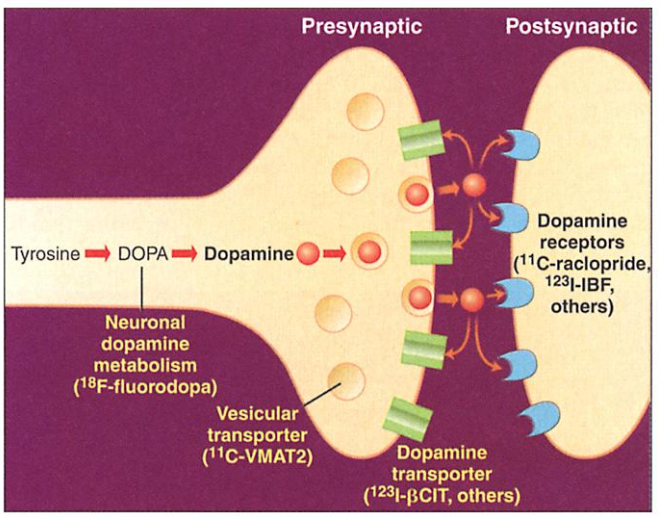
In 1819, when James Parkinson described the features of what was eventually called Parkinson's disease (PD), he noted that "unaided by previous inquiries immediately directed to the disease, and not having the advantage in a single case of that light which anatomical examination yields, opinion and not facts can only be offered (*1*)." He was referring to the light of a pathologic examination. It is doubtful that he could have imagined that imaging of the brain in live patients would one day provide a picture of the neurochemical pathology of neurodegenerative diseases such as PD or Alzheimer's disease (AD). In vivo imaging of the brain is a powerful tool for monitoring the chronic time course of these disorders—from preclinical through diagnosis to end-stage disease—and for assessing the potential of therapeutics that might interfere with the disease process.

Diverse imaging methods have been successfully applied to neurological disorders. Magnetic resonance imaging (MRI), which provides views of anatomic or structural brain abnormalities, has been especially useful for assessing the effects of, for example, stroke or multiple sclerosis (*2, 3*). Single photon emission computed tomography (SPECT) and positron emission tomography (PET), imaging techniques that measure brain chemistry, are well-suited for assessing biochemical abnormalities in patients with neurodegenerative disorders (*4*).

Imaging Technology

SPECT and PET use specific radioactively labeled ligands (radioligands) to neurochemically tag either normal or abnormal molecules such as neurotransmitter receptors in the brain. Depending on the pharmacokinetics, selectivity, and affinity of the radioligand for its target molecule, radioactive probes provide a means for sensitive quantitation of neurochemical changes in the brain. The past decade has seen rapid development of SPECT and PET detection devices (cameras). Improvements in signal detection and image reconstruction have made SPECT and PET imaging easier to use and more reliable. Both techniques use devices to detect the radioactivity emitted by the injected radioligand and to reconstruct three-dimensional tomographs of the distribution of radioactivity in the brain.



Imaging the brain. Molecular targets of radioligands on the pre- and postsynaptic membranes of dopaminergic neurons (DA) in the nigrostriatal pathway (which is affected in Parkinson's disease, PD). Radioligands (in parentheses) used to image the brains of PD patients target, for example, components of the dopamine synthetic pathways, the vesicular transporter (VMAT2), the dopamine membrane transporter, or the dopamine receptor in the postsynaptic membrane.

The PET detection devices have greater sensitivity and spatial resolution than those for SPECT, but SPECT is cheaper and more readily available in nuclear medicine facilities. Radioligands for PET imaging have short half-lives (for example, ^{11}C has a $T_{1/2}$ of 20 min) and must be produced in an on-site cyclotron. In contrast, SPECT radioligands have longer half-lives (for example, ^{123}I has a $T_{1/2}$ of 13 hours) and can be more readily supplied commercially. The spatial resolution of a state-of-the-art PET camera is 3 to 5 mm (this is the minimum size of the brain region of interest needed for a signal to be detected); the spatial resolution for a SPECT camera is 6 to 7 mm. New PET and SPECT imaging techniques—including three-dimensional imaging coupled with voxel-wide image analyses and statistical parametric mapping—are providing less user bias and greater reproducibility than more traditional region-of-interest analyses.

For large clinical trials, SPECT continues to have an advantage over PET because of its wider accessibility, moderately lower cost, and the ready availability of its radioligands. Nonetheless, PET imaging with ^{18}Fluoro-deoxy-glucose (FDG)—which provides a measure of glucose uptake, an indicator of cellular metabolism—is now in wide clinical use, partially changing this equation.

Imaging of Radioligands

Radioligands target specific neurotransmitter receptors and can often identify subpopulations of neurons in the brain. In PD, dopaminergic neurons in the nigrostriatal pathway gradually die off, resulting in a decrease in the neurotransmitter dopamine and the emergence of motor impairments characteristic of the disease. Imaging of radioligands directed at the molecular components of the dopaminergic system has provided new insights into PD (see the figure) (*5–8*). These molecular targets include components of the dopamine synthetic pathways, the dopamine vesicular transporter (which packages dopamine into vesicles to facilitate its release from dopaminergic neurons into the synapse), the dopamine membrane transporter known as DAT (which removes dopamine from the synapse and recycles it back into the neuron), and the dopamine receptor in the postsynaptic membrane. Imaging with ^{18}F-DOPA, which reflects dopaminergic neuron synthetic function, or with radioligands for DAT (such as ^{123}I-βCIT) which reflect nerve terminal integrity, demonstrates that 40 to 50% of imaging uptake has been lost at the threshold of PD diagnosis. Previous estimates from studies of pathological changes in the PD brain suggested that a loss of up to 80 to 90% of the dopamine content of nigrostriatal dopaminergic neurons might be required before symptoms of PD appeared (*9–11*). These imaging data both clarify the natural history of PD and provide further impetus to the development of therapies that will protect the remaining 50% of nigrostriatal neurons not yet affected when symptoms of PD first arise.

As the molecular pathways of PD, AD, Huntington's disease (HD), and other neu-

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rodegenerative diseases are being elucidated, the spectrum of potential molecular targets for radioligands is increasing dramatically. For example, recent data suggest that uptake of a radioligand that binds to the serotonin receptor ($5HT_{1A}$) was reduced in the cortex of PD patients with associated depression, but not in those without depression (*12*). In PD patients with dyskinesias, uncontrolled involuntary movements that are a disabling side effect of chronic PD medication, striatal uptake of a radioligand that binds to the opioid receptor is reduced suggesting that abnormal opioid transmission may occur in dyskinetic PD patients (*13*). In AD, the lack of specific markers has largely limited PET and SPECT to imaging glucose uptake in different brain areas. However, the development of new radioligands that target the abnormal deposits of amyloid in the AD brain may provide a more specific imaging tool (*14*, *15*).

Biomarkers of Disease Progression

Perhaps the most important advantage of brain imaging is that it can be used to assess disease progression in patients repeatedly throughout the course of their illness. The chronic, progressive, unpredictable nature of AD, PD, and related disorders has been perplexing and frustrating to patients, clinicians, and neuroscientists alike. Brain imaging is the best tool available to monitor the onset, severity, and progression of neurodegenerative diseases and to provide answers to the following questions:

1) What is the rate of neuronal degeneration in AD, PD, and related disorders?

2) What are the factors that determine the rate of neuronal degeneration?

3) Is there a preclinical period during which degeneration occurs, but clinical symptoms are not present?

4) Will putative neuroprotective or restorative drugs slow the rate of neuronal loss or perhaps even restore neuronal function?

Studies using serial imaging with ^{18}F-DOPA or radioligands for DAT to assess the rate of dopaminergic neuronal loss in PD patients show a progressive loss (from baseline) of approximately 10% per year. The rate of dopaminergic neuronal loss in these PD patients is about 10-fold greater than that in healthy older subjects (who gradually lose dopaminergic neurons as they age) (*16*, *17*). Although conclusions are limited by small sample sizes, these studies imply that neuronal degeneration in PD is an ongoing process originating about 5 to 10 years before development of symptoms of the disease.

Longitudinal imaging studies that enable evaluation of patients repeatedly over a prolonged period have transformed therapeutic studies of potential neuroprotective and restorative drugs. Imaging provides an essential objective endpoint for measuring changes in neuronal loss. Although imaging outcomes must be complemented with enduring clinical improvements, imaging has become necessary (although not sufficient) to demonstrate a convincing disease-modifying effect of drug treatment. Currently, there are many candidate disease-modifying drugs in development. For example, ongoing or planned clinical trials are using imaging to assess the effects of L-DOPA, dopamine agonists (pramipexole, ropinorole, pergolide), glutamatergic agents (riluzole and ramacemide), immunophilin ligands, and mitochondrial drugs (Coenzyme Q) on disease progression in PD, HD, and related disorders (*18*, *19*).

Preclinical Imaging

The optimal time to initiate neuroprotective interventions is during the preclinical period of the disease, when neuronal de-

generation has begun, but damage is not yet sufficient for symptoms to be manifest. The problem is that our ability to identify these preclinical "patients" is currently very limited. The most useful strategy has been to identify "at risk" groups and to search for preclinical neurodegeneration in these enriched populations. Molecular genetics has been most valuable in identifying at risk groups who are more likely to eventually develop disease (*20*). HD provides the best example of a neurodegenerative disorder with a known at risk genotype, but a variable phenotype (that is, the onset and severity of symptoms differ from patient to patient). Imaging of the dopamine D_2 receptor in striatal neurons, known to be selectively vulnerable in HD, with ^{11}C-raclopride may identify those at risk subjects who have begun to show signs of neuronal loss, but as yet show no symptoms of the disease (*21*). Similarly, imaging either unaffected family members in rare kindreds that have an inherited form of PD or AD or the unaffected twin of subjects with PD has shown that some at risk individuals have brain imaging abnormalities (as revealed by changes in ^{18}F-DOPA or glucose metabolism) prior to the appearance of symptoms (*22*, *23*). As molecular genetics expands the genotypes of neurodegenerative disease patients (with the identification of more susceptibility genes and at risk groups), it will be crucial to establish the time of onset and course of preclinical progression in these individuals, who represent the earliest disease phenotype.

The Future

The future of brain imaging shines bright. The explosion of information from the human genome project, in particular, and from molecular neuroscience, in general, creates a dizzying array of potential molecular targets with which to probe the brain's chemistry. Although current radioligands probe neurotransmitters and their receptors, new ligands will be developed that can probe different steps in the neurochemical pathways of cell death, signal transduction, and inflammation. As simpler tools to screen large populations are developed to identify preclinical at risk individuals, neurotransmitter receptor imaging will be widely used to establish and monitor the onset and progression of neuronal loss. Finally, as treatments become available that interrupt the pathological processes initiating and promoting disease, precise information about an individual's neurochemical status will lead to tangible improvements in clinical management.

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