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Molecular brain imaging: recent advances in relation to pathology and treatment

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Introduction

Molecular imaging of the brain using nuclear medicine techniques such as single-photon emission tomography (SPECT) and positron emission tomography (PET) has developed rapidly over the last decade, due to major advancements in radioligand development and imaging systems. This development has been particularly important in the context of neurodegenerative disorders. Advancement in PET technology, in combination with the development of new radioligands targeting specific pathological abnormalities, such as amyloid plaques or tau aggregates, has provided new tools for better examination of neurodegenerative disorders in vivo.

Amyloid imaging

At present there are several radioligands for imaging A with PET. In addition to [11C]PIB that has been the first to be introduced for amyloid imaging there are new 18F-labelled radioligands available for more routine clinical use. Florbetapir (Amyvid, Eli Lilly and Company), flutemetamol (Vizamyl, GE Healthcare) and Florbetaben (Neuraceq, Piramal Imaging) have received approval from FDA. Amyloid imaging can be used clinically in patients with persistent or progressive cognitive impairment or in patients with unclear or atypical dementia syndrome to confirm or rule out the presence of A pathology. In such cases the presence or absence of A pathology can help establishing the correct treatment for the patient. Clinical trials with immunotherapy for Alzheimer´s disease are ongoing. In such trials, amyloid imaging can be used as marker to demonstrate target engagement and also as enrichment tool to include in the trials only those patients with confirmed A pathology in vivo.

Tau imaging

In Alzheimer´s disease, amyloid plaques accumulate extracellularly whereas aggregates of hyperphosphorylated tau accumulate intracellularly. It is well known that tau deposition has better correlation with dementia severity than amyloid deposition and tau aggregates are topographically distributed differently as compared with amyloid plaques, accumulating selectively in the hippocampus. At present, there are radioligands for imaging tau that have shown promising results in first human studies. [11C]PBB3 is a tau radioligand that binds to both isoforms of tau, 3R and 4R. This radioligand has been shown to image both AD-type and non-AD type of tau and enables the detection of tau pathology in AD and tauopathies such as progressive supranuclear palsy and corticobasal degeneration. Other tau radioligands such as [18F]T807 and [18F]THK5117 have shown promising results in vivo in AD patients. Future studies are needed to assess whether these tracers can be useful as diagnostic tools or as markers in clinical trials aimed at targeting hyperphosphorylated tau aggregates.

Movement disorders

Other neurodegenerative disorders associated to specific pathological abnormalities are Parkinson´s disease and Huntington´s disease. The pathological hallmark of Parkinson´s disease is the formation of aggregates of alpha-synuclein in Lewy bodies. At present, there are no radioligands that show selectivity for alpha-synuclein, but the search of suitable imaging probes for alpha-synuclein is an area of intensive research. Degeneration of the nigrostriatal dopaminergic projection is a pathological feature of degenerative parkinsonism. Markers for dopaminergic terminals such as the dopamine transporter or the vescicular monamine transporter type 2 are suitable imaging targets for in vivo assessment of dopaminergic degeneration. Radioligands for these pre-synaptic targets, such as [123I]FP-CIT (DaTSCAN, GE-Healthcare) or [18F]FP-DTBZ (AV-133, Ely Lilly) are suitable imaging tools for the assessment of nigrostriatal degeneration. These radioligands can be used to examine the presence of degenerative parkinsonism in patients with unclear diagnosis and to identify those patients with dopaminergic deficit that can be enrolled in clinical trials of neuroprotection. In Huntington´s disease, the presence of intracellular aggregates of mutated huntingtin is a pathological feature of the disorder that is characterized by the loss of medium-sized spiny neurons of the striatum. Although radioligands for imaging mutated huntingtin are not yet available, imaging targets of the dopaminergic system, such as D1 and D2 receptors, can be used to assess the integrity of the striatal neurons. Another important target in HD is the phosphodiesterase 10 A (PDE10A) enzyme. PDE10A is highly expressed in medium-sized spiny neurons. Recent PET studies with different PDE10A radioligands have shown that PDE10A is severely

affected in HD patients already at a pre-manifest stage of the disease. Clinical trials aimed at specifically targeting PDE10A enzyme are ongoing and future trials are under design to specifically target mutated huntingtin. In this context, PDE10A imaging can be a suitable marker for the assessment of the effect of lowering huntingtin in HD.

Conclusions

The development of radioligands for A has contributed to major changes in molecular neuroimaging, providing tools for the in vivo examination of disease pathology. The field is expanding and new pathological imaging tools are under development. The discovery of new tools to directly examine the pathological abnormalities associated with major neurodegenerative disorders will likely provide biomarkers of great utility in the clinical setting and for optimal design and evaluation of treatment efficacy in clinical trials.

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