Invited Article

PET-Based Molecular Nuclear Neuro-Imaging

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Molecular Nuclear Neuro - Imaging in "CNS" drug discovery and development can be divided into four categories that are clearly inter-related.(1) Neuroreceptor mapping to examine the involvement of specific neurotransmitter system in CNS diseases, drug occupancy characteristics and perhaps examine mechanisms of action;(2) Structural and spectroscopic imaging to examine morphological changes and their consequences;(3) Metabolic mapping to provide evidence of central activity and "CNS fingerprinting" the neuroanatomy of drug effects;(4) Functional mapping to examine disease-drug interactions. In addition, targeted delivery of therapeutic agents could be achieved by modifying stem cells to release specific drugs at the site of transplantation('stem cell pharmacology'). Future exploitation of stem cell biology, including enhanced release of therapeutic factors through genetic stem cell engineering, might thus constitute promising pharmaceutical approaches to treating diseases of the nervous system. With continued improvements in instrumentation, identification of better imaging probes by innovative chemistry, molecular nuclear neuro-imaging promise to play increasingly important roles in disease diagnosis and therapy. (Korean J Nucl Med 38(2):161-170, 2004)

Key Words: Molecular imaging, Neuroimaging

Introduction

1. Functional Neurogenomics : Gene expression tomography

The comparison of gene expression profiles for the cerebral cortex of humans, chimpanzees, and rhesus macaques by using quantitative RT-PCR, cDNA arrays, and in situ hybridization demonstrated that surprisingly, most differences between the brains of humans and non-human primates involved up-regulation, with ~ 90% of the genes being more highly expressed in humans. By contrast, in the comparison of human and chimpanzee heart and liver, the numbers of up- and down-regulated genes were nearly identical.[1] Progress in DNA microarray studies will translate into arrary-based disease classification schemes and help optimize therapy for individual patients based on gene expression patterns or their genetic background('Pharmacogenomics').[2] For instance, the Autism Genetic Resource Exchange (www.agre.org) is the world's first collaborative gene bank for autism, sponsored by Cure Autism Now. A novel Magnetic Resonance(MR) probe of C_3F_7 tagged 5-Hydroxy-triptophan was developed and administered into ova without embryotoxicity for investigating neural development.[3] Two new approaches, voxelation and gene expression tomography (GET) of multiplex acquisition of gene expression patterns, provide the genomic scale information which is likely to help achieve the ultimate goal of understanding how the conceptual wiring diagram of the genome gives rise to the neuronal wiring diagram of the brain(www.vh.org/Providers/Textbooks/BrainAnatomy/BrainAnatomy. html).[4-6]

2. RNA interference: Large-scale genetic screens possible in human cells?

RNA interference(RNAi) silences a target gene through the specific destruction of that gene's messenger RNA (mRNA), the intermediary molecule between DNA and mRNA is central to the technique: when double strand DNA(ds DNA) with identical sequences to a specific mRNA is introduced into cells, the mRNA is recognized and degraded by a multiprotein body called the RNA-inducing silencing complex. More recently, with small interfering and

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short hairpin RNAs(shRNAs) as the gene silencers, RNAi has begun to do same job in mammalian cells.[7]

3. Approaches to optimize the discovery of CNS receptor imaging probes : Society of Non-Invasive Imaging in Drug Development(SNIDD)

Substance P(SP) - neurokinin 1(NK_1) receptor pathways have been implicated in the pathophysiology of emesis and depression. Imaging SP NK_1 receptor in the living brain using PET in the SP antagonist(SPA) program, a tracer [^{18}F] SPA-RQ was chosen for PET studies on the basis of several criteria including high affinity for the NK_1 receptor, low nonspecific binding, and good blood-brain barrier(BBB) penetration. PET receptor occupancy studies in rhesus monkeys and humans predicted that very high levels of central NK_1 receptor occupancy(>90%) were associated with therapeutically significant antidepressant and antiemetic effects.[8] Finally, clinical studies demonstrated that treatment with the SPA(NK_1 receptor) Aprepitan(also known as MK-0869) significantly improves depression symptoms and reduce the incidence of chemotherapy-induced nausea and vomiting.[9]

4. Combined cell and gene therapy: 'Therapeutic cloning' - 'Nuclear transplantation'

There are two possible mechanisms of stem cell-induced host recovery, direct replacement of host neurons and glia, or protection and regeneration of the host nervous system.[10] South Korean study of derivation of human embryonic stem cells from a cloned blastocyst, represents a significant step in a long journey to the cure of diseases that involve the loss of a particular cell type-disease such as type 1 diabetes and Pakinson's disease.[11-13] The isolation of pluripotent human embryonic stem cell(ES) and breakthrough in a somatic cell nuclear transfer(SCNT) in mammals have raised the possibility of performing human SCNT to generate potentially unlimited sources of undifferentiated cells for research. This concept, known as 'therapeutic cloning,' refers to the transfer of the nucleus of a somatic cell into an enucleated donor oocyte. When applied in a therapeutic setting, these cells would carry the nuclear genome of the patient; therefore, it is proposed that directed cell differentiation, the cells could be transplanted without immune rejection.

5. Stem cell plasticity: One cell for all disease ? 'Transdifferentiation' or 'Transdetermination'

Recent reports have shown that cell fusion is a plausible means by which adult cells adopt other phenotypes.[14] Neural stem cells were demonstrated into virtually every cell type when they were injected into blastocysts in vivo or cultured in vitro with differentiating embryonic stem cells.[15] From a culture of pleuropotent stem cells in vitro from adult cells(bone marrow cells) by nurturing them with embryonic stem cells, transplantation of adult bone marrow cells has generated unexpected phenotypes in vivo, including muscle cells, liver cells, brain cells and others.[16]

Alzheimer's Disease

1. Potentially reversible conditions in memory clinic patients

Adjusted for the changing structure in the age distribution of populations over time, the number of cases of dementia in the developed world rise from 13.5 million in 2000, to 21.2 million in 2025, and 36.7 million in 2050. If dementia prevalence doubles with every five years of age, then prevalence would be halved by delaying the onset of AD by five years.[17] The approval of acetylcholinesterase(AChE) inhibitors for the treatment of AD(Metrifonate,[18] Donepezil,[19] and Rivastigmine[20]) increased the focus on diagnostic assessment of patients with dementia, particularly in the early stage, using PET with [^{18}F] FDG as a surrogate marker(www.loni.ucla.edu). To maximize the benefits of AchE inhibitors, treatment should begin as early as possible, ideally in patients with very mild AD.[21] After passing the BBB, N-[^{11}C] methylpiperidin-4-yl acetate ([^{11}C]MP4A) is hydrolysed by AChE and is trapped within the brain in proportion to regional AChE activity. Hippocampal AChE activity is only slightly reduced in mild cognitive impairment and early AD and so the value in vivo AChE measurements in detecting the early AD process is limited.[22,23]

As a novel therapeutics, Galantamine acts at a site on the AchR that is different from the Ach binding site, it is referred

to as an allosteric potentiating ligand.[24-26]

2. APOE genotype and PET brain imaging on preclinical prediction

PET has been used to study Alzheimer's Disease(AD) as well as various stages of age-related cognitive decline such as Age-Associated Memory Impairment(AAMI)[27] and Mild Cognitive Impairment(MCI).[28,29] Studies of cerebral glucose metabolism using ^{18}F-FDG have demonstrated that regional metabolic patterns vary among different forms of degenerative dementia and that these patterns can predict clinical progressions and definitive diagnosis with a sensitivity of 94% and specificity of 76%.[30] Multicenter quantitative FDG PET imaging data base of more than 1000 subjects is available on 'Network for Efficiency and Standardisation of Dementia Diagnosis'(www.nest-dd.org). From the complexity of AD genetic research, National Institute of Mental Health(NIMH)-AD Genetic Initiative resulted that only one risk factor, a common polymorphism in the Apolipoprotein E gene(APOE), has been consistently found in several independent samples. When FDG-PET scan measures are combined with APOE-4 measures of AD genetic risk, parietal, temporal, and posterior cingulated deficits were observed in middle-aged people and older adults at genetic risk.[31]

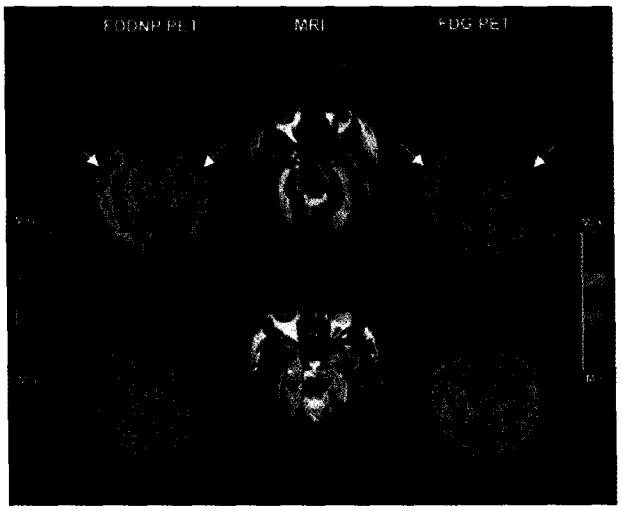

Fig. 1. Multimodality in vivo imaging of an AD patient and a control. The (^{18}F) FDDNP and PDG images of each stage are coregistered to their MRI images. Areas of FDG hypometabolism are matched with the localization of neurofibrillary tangles and senile plaques resulting from (^{18}F) FDDNP binding(marked arrows). The same brain regions exhibited atrophy(as shown with MRI) in the AD patient. The colorbar represents the scaling of the (^{18}F) FDDNP and FDG images.(From ref. 33.)

3. Tau phosphorylation, tangles, and neurodegeneration: Chicken or Egg?

Pathological deposition of the microtubule(MT)-associated protein tau, in the form of hyperphosphoylated inclusions or filamentous neurofibrillary tangles(NFTs), is one of the defining features of adult-onset neurodegenerative diseases such as AD, progressive supranuclear palsy(PSP), frontotemporal dementia and parkinsonism linked to the chromosome 17(FTDP-17). Current evidence shows that the known FTDP-17-causing tau mutations either disrupt MT binding or affect tau splicing, leading to tau isoform imbalance and increase in free tau unbound to microtubules. Since tau polymerization into filaments is concentration dependent in vitro, this provides an obvious common mechanism for tau aggregation and NFT formation in vivo.[32] Studies of amyloid-ß protein metabolism are promising preclinical drug candidates for treatment of AD. Major therapeutic candidates aimed at altering Aß metabolism include secretase inhibitors(enzyme inhibitors that prevent the production of Aß) and immunotherapy(both active and passive immunization).

4. Amyloid plaque imaging: Novel diagnostic and therapeutic tools

Human studies aimed at validating the use of a radiolabeled ligand as a PET amyloid imaging agent. This ligand is known as [^{18}F] FDDNP(2-Dialkylamino-6-Acylmalonitrile Substituted Naphthalenes)(UCLA. USA),[33,34] [^{11}C] 6-OH-BTA(Benzo Thiazole Anilines)(Univ of Pittsburg. USA: Uppsala Univ. Sweden),[35] and ^{123}I-IMPY(Thioflavin Derivative)(Univ of Penn. USA).[36] [^{18}F] FDDNP-PET molecular imaging for senile plaques(SPs) and NFTs(Fig. 1) provides a disease- specific, in vivo imaging tool for determination of localization and load for these AD-related lesions, however, its in vivo specificity has not yet been clarified owing to its low clearance from white matter.[37]

5. Neuronal Cyclooxygenase -2 in cell cycle and clinical progression

Neuronal Cyclooxygenase(nCOX-2) is induced by glutamate

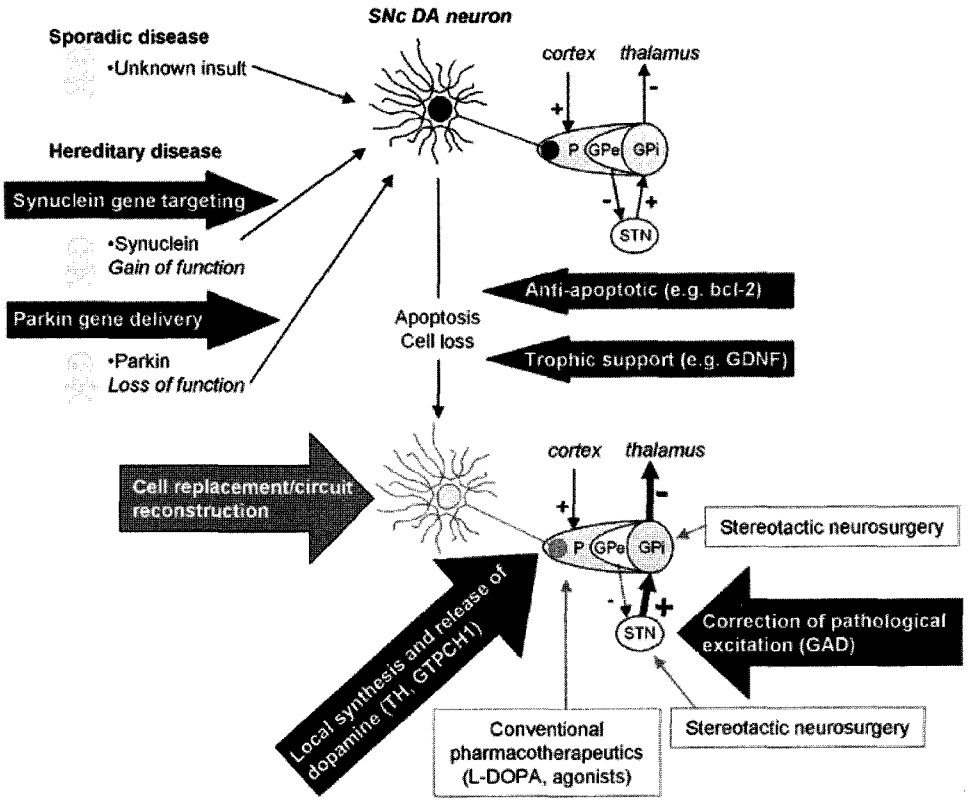

Fig. 2. *Gene therapy strategies for PD. The putative events and functional consequences involved in* loss of SNc neurons are depicted. The complex pathogenetic and pathological cascade provides several candidates targets for molecular intervention, which are labeled with black arrows and white text. In addition, alternative strategies to gene delivery, involving functional neurosurgery, cell transplantation and neuropharmacology are shown for contextual comparison. Abbreviations: P, putamen; Gpe, external segment of globus pallidus; Gpi, internal segment of globus pallidus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase; GTPCH1, GTP-cyclohydrolase-1.(From ref. 50)

and aggregated Aß peptides may promote cell cycle activities by decreasing the expression of the CDK4,6 inhibitor p18, possibly leading to an unsuccessful attempt to re-enter the cell cycle, influencing caspase activity and neuronal death. Therefore, nCOX-2 responsive cell cycle activities, possibly facilitating the transition of resting neurons from the G_0 into the G_1 phase, represent an important target for neuroprotection by NSAIDs.[38,39] McCarthy et al. prepared a positron-labeled COX-2 probe by synthesizing an ^{18}F-labelled analog of the COX-2 inhibitor SC-58125,[40] a molecule with a para-fluoro substituent that is otherwise closely related to celecoxib (Celebrex).[41]

Parkinson's Disease

Parkinson's Disease(PD) is an attractive target for CNS gene and/or cell therapy and has been the archetypal model of neural transplantation(Fig. 2).

1. Deep Brain Stimulation : Differential modulation of subcortical target and cortex

The combination of electrical deep brain stimulation (DBS) with functional imaging using parametric $H_2{}^{15}O$ PET offers a unique model for tracing brain circuitary and for testing the modulatory potential of electrical stimulation on a neuronal network in vivo.[42-44] Subthalamic nuclei(STN) stimulation increased blood flow in midbrain(including STN), globus pallidus, and thalamus, primarily on the left side, but reduced blood flow bilaterally in frontal, parietal, and temporal cortex. These data suggested that STN stimulation increases firing of STN output neurons, which increases inhibition of thalamocortical projection, ultimately

decreasing blood flow in cortical targets.[45]

2. Transplantation of embryonic dopamine neurons for severe PD

Well-executed clinical trials of cell transplant therapy using cultured mesencephalic tissue from embryos with ^{18}F-fluorodopa PET showed human embryonic dopamine-neuron transplants survive in patients with severe PD without impairing cognition and result in some clinical benefit in younger but not in older patients.[46] These findings suggest that patient age does not influence graft viability or development in the first postoperative year but, host age may influence the time course of the downstream functional changes that are needed for clinical benefit to occur.[47] However, 56% of transplanted patients developed dyskinesia that persisted after overnight withdrawl of dopaminergic medication. Off-medication dyskinesia after transplantation thus may reflect partial, but inadequate, graft survival that is sufficient to produce, store, and release low levels of dopamine for a prolonged period of time after a dose of L-dopa, but not sufficient to induce an antiparkinsonnian response. Fetal nigral transplantation currently cannot be recommended as a therapy for PD.[48]

3. New candidate target genes: Isolation in rare genetic forms in PD

Rare genetic forms have allowed isolation of genes involved in their pathogenesis, and thus highlighted cellular pathways that may be vulnerable in dopaminergic neurons and form potential targets for molecular intervention in PD. Mutations have been described in the gene encoding α-Synuclein, resulting in autosomal dominant PD. Aggregates of α-Synuclein comprises a major component of Lewy body, which is the pathological hallmark of the common sporadic form of PD. A second form of familial PD is autosomal recessive, and results from mutations in the gene encoding Parkin, a ubiquitin ligase. Interestingly, α-Synuclein is a substrate of Parkin,[49] linking two dissimilar proteins into a common functional pathway. Using α-Synuclein transgenic mice, overexpression of β-Synuclein prevented aggregation of α-Synuclein and the resulting abnormal phenotype, thus β-Synuclein or Parkin gene delivery might be effective measures to disrupt the pathogenic cascade causing neurodegeneration.[50] Pathogenic mutations resulting in a PD phenotype have been described in two other genes: DJ-1[51] and NR4A2, encoding Nurr-1, a nuclear receptor.[52]

4. Gene therapy progress in PD

1) Inhibition of apoptosis by gene delivery prevents development of the disease phenotype in animal models: Anti-apoptotic(bcl-2), Neuronal apoptosis inhibitor protein(NAIP),[53] Prevention of apoptotic protease-activating factor-1(apaf-1)-dependent activation of caspase 9.[54]
2) Transgene-mediated expression of glial cell line-derived neurotrophic factor(GDNF) may prevent progression after an initial insult, and may even be restorative in animal models: Trophic support.[55]
3) Combination of antiapoptotic and GDNF gene therapy protects dopaminergic neurons against a toxic insult, more effectively than either intervention alone.[56]
4) Transgene-mediated production of the inhibitory neurotransmitter γ-amino butyric acid(GABA) in neurons of the subthalamic nucleus ameliorates the behavioral phenotype and may be neuroprotective, in an animal model: Glutamic acid decarboxylase(GAD; rate-limiting enzyme for synthesis of GABA).[57]
5) Delivery of transgenes encoding enzymes involved in dopamine biosynthesis enhances dopamine production in the striatum: Tyrosine hydoxylase(TH ; rate-limiting enzyme for dopamine formation), GTP-cyclohydrolase I(GCH1; for cofactor synthesis).[58]
6) Stem cells may be driven to differentiate into functioning dopaminergic cells by genetic modification.[59-61]
7) Isolation of genes impaired in rare genetic forms of PD has allowed generation of new animal model and identification of new candidate targets for intervention: Synuclein gene targeting(gain of function),[62] Parkin gene delivery(loss of function).[63]
8) One human gene therapy trial commenced in PD: Correction of pathological excitation(GAD).[64]
9) The optimal vector remains uncertain.

5. Glutamic Acid Decarboxylase gene therapy to subthalamic nucleus in PD

Transduction of STN neurons with Glutamic acid decarboxylase(GAD), the rate-limiting enzyme for synthesis of the inhibitory neurotransmitter GABA, using an adeno-associated virus vector, resulted in synthesis and activity-dependent release of GABA from STN nerve terminals.[57] In all 12 patients with asymmetric disease underwent unilateral STN stimulator implantation. The trial is a dose-escalation safety study, and as approved by US Food Drug Administration three cohorts of patients received between 10^{11} and 10^{12} particles of rAAV (recombinant Adeno-Associated Virus) GAD at the time of STN stimulator implantation. The assessors monitor the patients' clinical state and PET scans. In the worst case, if GAD gene transfer has an unanticipated deleterious effect, then the STN can be either electrically silenced or ablated, both standard treatments for PD, using the stimulator leads without additional surgery.[64]

6. Stem Cells: Replacement or Protection in PD

Using an improved paradigm, directed differentiation of mouse ES cells into functional dopamine neurons has been achieved with transfection of nuclear receptor related-1 followed by a multi-step in vitro growth condition-guided approach.[52] In addition to neural replacement, undifferentiated neural stem cells might act as chaperones that offer neuroprotection and mediate rescue of degenerative host populations. In some cases, this has been linked to GDNF, a potent growth factor with known 'dopaminotrophic' effects.[65]

7. Cell / Gene therapy prospect in PD

1) Development of presymptomatic diagnostic tests will facilitate neuroprotective studies
2) Better understanding of the pathogenesis may lead to the development of improved animal models that more closely resemble the human disease
3) Studies may broaden their scope to include the important nonmotor manifestations of PD such as depression, cognitive and autonomic dysfunctions
4) Further characterization of ES and adult stem cell populations will establish whether ex vivo transduction can drive their differentiation into dopaminergic neurons in a therapeutically useful way[66]
5) Well-designed clinical trials for PD gene therapy may take their lead from cell transplantation trials

Stroke

1. Beyond Antithrombotics: Ischemic stroke prevention, pathogenesis and therapy

The realization that atherosclerosis is an inflammatory disease has led to search for new stroke and cardiovascular disease risk factors and treatments. Beyond the traditional antithrombotic agents, statin agents, angiotensin-converting enzyme inhibitors(ACEI),[67] and vitamins may prove to be important to the armamentarium for stroke prevention (http://neuro-oas.mgh.harvard.edu/stopstroke/research_list.htm).[68] A novel diagnostic classification system was recently described for acute ischemic cerebrovascular syndrome(AICS) that defines the degree of diagnostic certainty by integrating neuroimaging and laboratory data with prior clinically based classification schemes to define 4 categories into Definte, Probable, Possible and Not AICS.[61] The narrow time window for intravenous thrombolytic therapy with recombinant tissue plasminogen activator(r-tPA) or intraarterial thrombolytic

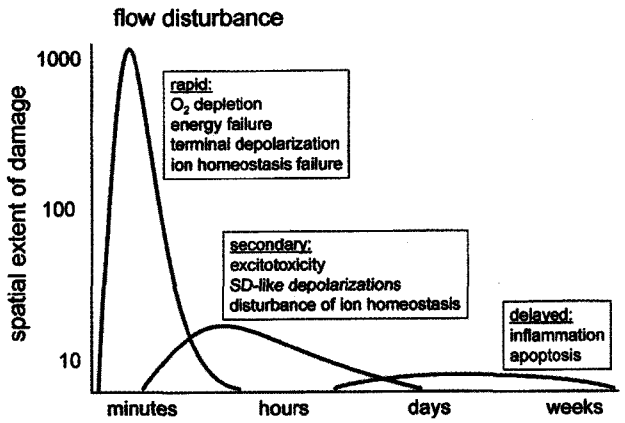

Fig. 3. Hypothetical diagram of spatial extent(arbiturary logarithmic scale) and temporal course of development of ischemic damage. Rapid effects of flow disturbance cause the bulk of the final infarct, while secondary and delayed effects are responsible for relatively little additional damage. SD indicates spreading depression.(From ref. 71)

therapy (within 3-h and 6-h of symptoms, respectively, by FDA approval) necessitates prehospital field initiation of Mg sulfate as neuroprotective therapy(FAST- MAG trial : Fast Administration of Stroke Treatment- Magnesium)(Fig. 3).[70,71]

2. Beyond Mismatch: Paradigm shifts

Diffusion weighted MR imaging(DWI) provides a measure of tissue bioenergetic compromise and Perfusion weighted MR imaging(PWI) a measure of hemodynamic compromise. DWI is an echo-planar imaging(EPI) - based technique that measures the random motion of water molecules(i.e., diffusion). Tissues in which water mobility is restricted appear dark on parametric apparent diffusion coefficient(ADC) maps. Use of newer ADC imaging techniques, such as fluid-attenuated inversion recovery(FLAIR) ADC, may improve overall prediction ability of isolated ADC thresholds alone even further. PWI using injection of an exogenous contrast agent(Gd-based chelate) to act as a T2* contrast agent during its first pass through the cerebral vasculature, is currently widespread performed. The contrast agent causes a transient decrease in signal intensity(T2* - shortening susceptibility effect), proportional to the concentration in a given region. The technique is known as dynamic susceptibility contrast(DSC) imaging. A significant diffusion-perfusion mismatch may be present up to 24 hours or more from symptom onset. There now are sufficient data to support paradigm shifts in a variety of central tenets regarding MRI and the ischemic penumbra(Fig. 4).[72,73] The first major challenge to the mismatch model is differentiation of true penumbra from tissue experiencing benign oligemia. The second challenge to the mismatch model involves differentiation of the true penumbra from the ischemic core.

3. Beyond Tissue Plasminogen Activator: Mechanical intervention in Acute Stroke

Mechanical interventions in acute ischemic stroke promise to provide emergency physicians with tools such as clot retriever devices, percutaneous ballon angioplasty, and laser thrombolysis, etc. to treat patients in whom conventional thrombolysis might be ineffective or contraindicated.[74] Penumbral ischemic brain injury can be averted or even substantially reversed if reperfusion of the affected territory occurs as long as 6 hours or more after stroke symptom onset after intra-arterial recombinant Pro-urokinase(Prolyse) for Acute Cerebral Thromboembolism(PROACT Trial).[75-77]

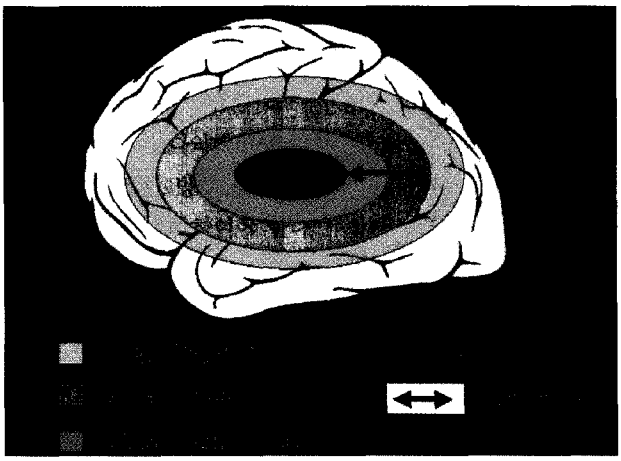

Fig. 4. Modified view of MRI-defined ischemic penumbra in which the penumbra equals not only regions of diffusion-perfusion mismatch but also a portion of the diffusion abnormality itself.(From ref. 72)

4. Penumbragram

Mapping the penumbra and core with novel PET approaches is an area of considerable interest. Using the hypoxia marker ^{18}F-labeled fluoromisonidazole(FMISO), Markus and colleagues validated a quantitative voxel-based 3-dimensional model of high FMISO uptake assumed to represent the penumbra ('penumbragram') and showed that the evolution of the penumbra occurs from central to peripheral regions with the distribution predominantly superior and mesial in the cortex.[78] In 34 patients with large middle cerebral artery(MCA) stroke, comparison of the value of ^{11}C-labeled flumazenil PET mapping of core and penumbra was performed within 24 hours of onset, with intensive neuromonitoring including ICP, Pt_{O2}, lactate, pyruvate, and glutamate to predict the development of malignant brain swelling. These data clearly showed that PET was a better early predictor of malignant MCA infarction than neuroimonitoring.[79] Having imaging-based clinically applicable early reliable predictors of malignant MCA infarction and early neurochemical monitoring of non-transmitter amino acids with microdialysis, would allow craniectomy to be performed within 24 hours to prevent secondary ischemia from increased intracranial pressure.[80]

5. Carotid artheromatous plaque imaging

An inflamed potentially vulnerable atheromatous carotid plaque may be imaged with ^{18}F-FDG PET, and a mononuclear inflammatory cells in experimental plaque take up MRI-detectable ultra small superparamagnetic iron oxide particles(SPIO) injected into the circulation. By ^{18}FDG PET and co-registered CT imaging, Rudd et al., had confirmed that ^{18}FDG accumulates in human carotid artery atherosclerotic plaques, the estimated net ^{18}FDG accumulation rate(plaque/integral plasma) in symptomatic lesions was 27% higher than in contralateral asymptomatic lesions and the majority of deoxyglucose accumulates in macrophage-rich areas of the plaque, predominantly at lipid core/fibrous cap border of the lesions on tritiated deoxyglucose autoradiography.[81]

6. Stem cells as a potential treatment of stroke

It has long been believed that the adult mammalian CNS is incapable of significant self-repair or regeneration. Following transient forebrain ischemia which induced selective degeneration of hippocampal CA1 pyramidal neurons, endogenous progenitors from the periventricular region and parenchyma produced new neurons that participated in hippocampal regeneration. Significant recovery levels were noted 28 days post-ischemia, and could be considerably enhanced(approximately 40% recovery from total neurons lost) by treatment with epidermal growth factor and fibroblast growth factor-2. Moreover, regenerated CA1 neurons survived for at least six months, integrated into the neuronal circuitary and formed functional synaptic connections; spatial cognitive performances could be improved at last time points with growth factor administration. As a therapy, however, application of potent mitotic growth factors to the brain has to be tempered by the possibility of stimulating overgrowth of new cells and tumor formation.[82] In a similar study, transient middle cerebral artery occlusion-induced stroke leads to increased cell proliferation in the adult rats, leads to a marked increase of cell proliferation in the subventricular zone. Stroke-generated new neurons, as well as neuroblasts probably already formed before the insults, migrate into the severely damaged area of the striatum, where they express markers of developing and mature, striatal medium-sized spiny neurons. Despite the promise of self-repair in the adult brain through generation of new neurons, the overall level of endogenous self-recovery in this study was very low, with an estimated 0.2% replacement.[83] Nevertheless, these findings have paved the way for an exciting area of research for novel therapeutic strategy for stroke in humans.

국문요약

분자영상은 살아있는 개체의 몸 속에서 일어나는 생물학적 반응이나 특정한 표적분자를 비관혈적이며 반복적으로 영상화하는 기술이다. 이를 위해서는 두 가지 기본 요소가 요구되는 바 하나는 관심 생물현상에 의해 농도나 분광특성이 변하는 분자영상용 추적자이며 다른 하나는 이런 추적자를 모니터링하는 장비이다. 분자 핵의학 영상기술은 이제 신경과학분야에서도 활발히 적용되고 있으며 신경관련 기초연구나 뇌질환 관련 신약개발에 이미 중요한 역할을 하고 있다. 최근에는 살아있는 개체에서 약제 투여가 뇌에 미치는 약물학적, 생리적 영향을 조사하는 데에도 이용되고 있다. 다가오는 미래에는 각종 뇌질환에서 특이적 표적을 공략하는 새로운 분자치료가 개발되어 뇌질환 치료에 혁명적인 변화를 가져올 것으로 예상되고 있다. 그 예로, 파킨슨씨 병과 같은 퇴행성 신경질환에 줄기세포를 이용한 자가수선, 신경보호, 약물분비 치료, 성장인자와의 병행치료 등이 개발되고, 유전자 치료도 이용될 것으로 보인다. 신경 분자 핵의학 영상은 이와 같은 새로운 뇌질환 치료기술의 개발에 있어서 뇌 안에서 일어나는 분자수준의 변화를 실시간으로 모니터링함으로써 관련연구에 크게 기여할 것으로 기대된다

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