脑血管疾病研究现状与前景

NAO XUEGUAN JIBING YANJIU XIANZHUANG YU QIANJING

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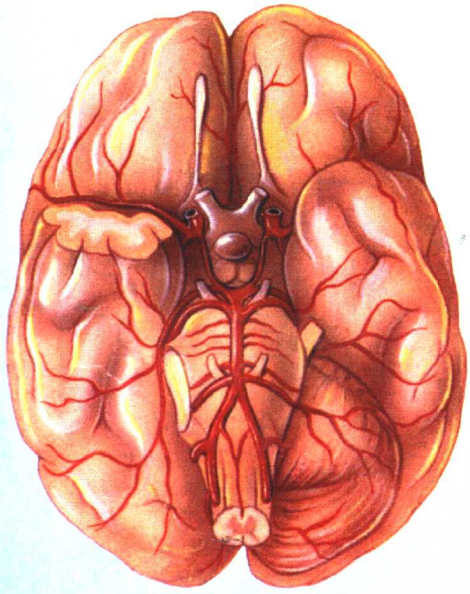

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内 容 提 要

内容涉及近年来发展很快地脑血管病研究技术、方法及取得的最新成果，如缺血性脑血管病早期或超早期溶栓、神经保护和神经营养治疗；动脉瘤的神经介入技术及临床研究现状；循证医学在脑血管病研究领域的应用及其所取得的研究成果；同时还介绍了一些国际上脑血管病研究的新观点、新技术和新方法，以开阔国内同行的思路和引起他们的注意。

读者对象：神经内外科医师、研究生和进修生。

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前　言

随着各种新技术、新方法的不断引进，脑血管疾病的研究进入了崭新的发展阶段，取得了令人瞩目的成就。基础研究取得的成就，使我们对缺血性脑血管病的病理生理机制的认识越来越深刻，已有一些研究成果用于指导临床实践。在临床研究方面，随着神经影像技术的发展，尤其是无创性影像技术的发展，如经颅多普勒超声技术、磁共振成像技术在脑血管疾病诊断中的广泛应用，使我们有可能筛选出一些早期甚至超早期溶栓治疗可能获益的病例，并对其治疗效果进行评价；缺血性卒中的神经保护和神经营养治疗也取得了令人鼓舞的成绩；广泛开展的神经介入疗法，使得一些以往无法直接手术的动脉瘤得到了有效处理，并取得了较好的临床结果。近年来，循证医学在脑血管疾病研究领域中也得到了广泛开展，这为客观评价临床试验提供了可靠的依据。一些新的药物，如他汀类、抗血小板聚集药物的应用，已使卒中再发的比例呈下降趋势。所有这些进展，与我国神经科学工作者的勤奋努力和紧跟国际发展的最新动态是分不开的，与我国一些专家学者们的开拓性研究也是分不开的。

《国外医学脑血管疾病分册》编辑部、全国脑血管疾病防治办公室和第一军医大学南方医院，将于2001年4月在广州主办国际脑血管疾病研究进展学术交流会，作为主办单位之一的《国外医学脑血管疾病分册》编辑部将会议征文编辑整理成书。这本书的内容基本上反映了我国近年来脑血管疾病研究的现状，其中的一些文章对脑血管疾病研究前景也有所反映。我们希望这本书的出版，能为我国脑血管疾病的基础研究和临床工作者提供一个交流的机会，为促进脑血管疾病研究的发展尽一点微薄之力。

这项繁杂的工作是编辑部的同志在日常工作以外完成的，由于时间比较仓促，其中必然会有一些缺点和错误，请各位同仁不吝赐教。

编　者

2001年2月

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INVITED REVIEW

Thrombolytic Therapy for Acute Ischemic Stroke

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The NINDS rtPA trial was the first acute ischemic stroke trial to unequivocally demonstrate that this disorder could be benefited by any therapeutic intervention[1]. In this trial, 624 carefully selected patients were randomly and blindly assigned to therapy with rtPA (0.9mg/kg) or placebo within 3 hours of stroke onset. Half of the patients were treated within 90 minutes of onset, a truly remarkable accomplishment by the investigators participating in the trial. The rtPA treated patients had an absolute improvement rate of 11-13% at 90 days when compared to the placebo patients on various outcome measures that evaluated both neurological and functional status. The rtPA treated patients had a symptomatic intracerebral hemorrhage rate of 6.4% (almost 1/2 fatal) within 36 hours of onset, while the rate was only 0.6% in the placebo group. Despite this early hemorrhagic risk, the 90-day mortality was 17% in the rtPA group and 21% in the placebo group. Subsequent analysis of the study data demonstrated that early CT demonstration of extensive edema or hypodensity, history of diabetes mellitus, and elevated baseline National Institute of Health Stroke Scale Score (NIHSS) were predictors of poor outcome[5]. The use of rtPA was associated with improved outcome in all stroke subtypes included in the study, in patients across the broad range of baseline stroke severity, and in all age groups. The initial analysis of the study data did not distinguish a difference in benefit of rtPA related to time of treatment initiation. However, in a subsequent analysis that adjusted for baseline severity of the neurological impairment an earlier time to initiation of therapy was associated with a more favorable outcome, demonstrating an inverse linear relationship between time to treat and the odds ratio of a favorable outcome[6]. The confidence interval for a favorable outcome crossed 1 in patients treated beyond 2 hours and 40 minutes after stroke onset, suggesting that treatment initiated beyond this time point may not be of proven efficacy.

Several post-marketing studies of i.v. rtPA are now available[7-15]. Patients were included in these studies using the general guidelines for treatment employed in the NINDS trial. The most important inclusion criteria were initiation of therapy within 3 hours of stroke onset. Most of the studies encompassed relatively small numbers of patients, ranging from 14-75. However several larger studies are available, including the study reported by Grond et al of 100 patients[11] and the STARS study of 296 patients[15]. The median time from stroke onset to initiation of rtPA therapy ranged from 124 minutes in the Grond study to 165 minutes in the STARS study. The percentage of patients achieving a modified Rankin Score of 0-1, the results defined as a favorable outcome in the NINDS trial, ranged from 34% to 57% although, in several of the reports day 90 data were not provided.

On the surface the rates of favorable functional outcome demonstrated in these post – marketing studies appears to be quite good, surpassing in some studies the 39% 0-1 Rankin rate at 90 days seen in the NINDS trial. These results must be interpreted cautiously because the baseline severity of the patients treated in these post-marketing studies was not as severe as in the NINDS trial. For example in the two largest post-marketing studies, the Grond study and the STARS study the median baseline NIHSS scores were 12 and 13, while in the NINDS trial the median baseline NIHSS score in the placebo group was 14 in part 1 and 15 in part 2. In other acute stroke trials where the baseline NIHSS score was 11, the percentage of patients achieving a Rankin score of 0-1 approximates 37%[13] and when the baseline NIHSS score was 13, 29% achieved this outcome[14]. Comparing the outcomes in the Grond and STARS studies to a placebo group with a similar degree of baseline severity demonstrates an absolute improvement rate of

3-6%, not the approximately 12% absolute rate of improvement observed with rtPA treatment in the NINDS trial. The post-marketing studies do however provide some encouraging data about the rate of symptomatic intracerebral hemorrhage. The percentage of patients experiencing this serious complication of thrombolysis ranged from 0-19% with only two studies observing double-digit rates of intracerebral hemorrhage. In the two largest studies, the intracerebral hemorrhage rates were only 4-5%. It therefore appears that expanding i.v. rtPA use into general practice is not associated with a substantially increased risk of intracerebral hemorrhage, if the guidelines for patient selection employed in the NINDS trial are followed.

Studies evaluating the efficacy of i.v. rtPA beyond the 3-hour time window were conducted. The first clinical trial to evaluate i.v. rtPA up to 6 hours after stroke onset was the European Cooperative Acute Stroke Study (ECASS-1)[14]. Patients were randomly and blindly assigned to rtPA (1.1 mg/kg) or placebo within the 6-hour time period after acute stroke onset in the middle cerebral artery territory. Predefined exclusion criteria included evidence of CT hypodensity or sulcal effacement involving more than 1/3 of the middle cerebral artery territory on the pretreatment CT scan. The overall results as analyzed in the intention to treat analysis of the trial were negative, but when protocol violators were excluded several outcome measures were better in the rtPA group. CT exclusion criteria (> 1/3 of the MCA territory showing early infarct signs) occurred in 63 of 109 protocol violators and these patients had a very high risk of symptomatic often-fatal intracerebral hemorrhages when they received rtPA. A second ECASS study was performed using the NINDS dose of rtPA, 0.9mg/kg and in this study the study investigators received better CT training to identify hyperacute CT changes indicative of early infarction[13]. Patients were again randomized up to 6 hours after stroke onset. In ECASS-2, the primary endpoint was the % of patients in the two treatment groups achieving a Rankin score of 0-1 and this outcome was observed in 40.3% of the rtPA treated group and 36.6% of the placebo group, a nonsignificant difference. Interestingly, the median baseline NIHSS scores were only 11 in the two groups. Therefore, the baseline severity of the stroke patients included in ECASS-2 was less than in the first ECASS study or the NINDS study, likely explaining in part the better outcome observed in the placebo group of this trial than in the other two i.v. thrombolysis trials. A post-hoc analysis of the ECASS-2 data demonstrated a significant difference between the rtPA treated group and the placebo group when the Rankin score was dichotomized into 0-2 and > 2. In this analysis, 54.3% of the rtPA patients achieved a 90-day outcome of 0-2, while only 46% of placebo patients had a 90-day Rankin score of 0-2. The difference between a score of 1 or 2 on the Rankin scale is not great and this result speaks to the inherent difficulties in determining the best outcome measure to employ in acute stroke studies. One other large i.v. rtPA study evaluating therapy initiated from 3-5 hours after stroke onset is available. In this study, Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS), the patients received 0.9 mg/kg of rtPA i.v. and the primary outcome measure was the % of patients achieving an NIHSS score of 0-1 at 90 days[15]. The study included 547 patients and the primary endpoint was almost identical in the two groups. The median baseline NIHSS score was 11 in the two groups and a day 90 modified Rankin of 0-1 was achieved in 42% of the rtPA group and 40% of the placebo patients. One positive result from the ECASS-2 and ATLANTIS trials was that the rate of symptomatic intracerebral hemorrhage was 8.8% and 7.0% respectively, not greatly increased from the 6.4% rate seen with rtPA in the 3-hour window NINDS trial.

There is a 0-6 hour thrombolysis trial that does demonstrate a significant treatment effect. This study, the i.a. PROACT-2 study, used recombinant prourokinase (r-proUK) delivered locally into an angiographically documented proximal middle cerebral artery thrombus with low-dose i.v. heparin[2]. In both the active treatment and placebo groups, the median time to treat in PROACT-2 was 5.3 hours and the median baseline NIHSS score was 17. The trial included 180 patients randomized 2:1 to r-proUK or placebo. At day 90, 40% of the r-proUk treated patients achieved the primary outcome measure of a Rankin score of 0-2, while only 25% of the placebo patients achieved this favorable outcome, $P = 0.04$. Secondary outcome measures also tended to be better in the r-proUK group. Symptomatic intracerebral hemorrhage within 24 hours occurred in 10.2% of the r-proUK group and 1.9% of control patients. Despite the early risk of symptomatic intracerebral hemorrhage, the 90-day mortality was almost identical in the two groups, 25% in the r-proUk group and 27% in controls. The PROACT-2 study demonstrates that

thrombolytic therapy can be effective when initiated up to 6 hours after stroke onset in carefully selected patients and should initiate additional attempts to successfully expand the time window for i.v. thrombolysis in acute ischemic stroke.

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INVITED REVIEW

Neuroprotection

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The premise of neuroprotective therapy for acute ischemic stroke is based upon the possibility to interfere with the cellular consequences of focal brain ischemia, i.e. the ischemic cascade. Neuroprotective therapy alone is dependent upon the delivery of such drugs to the ischemic penumbra where there is some residual blood flow. In animal stroke models, a wide variety of neuroprotective drugs demonstrated significant effects upon the ischemic tissue with the significant reduction of ischemic lesion volume. The main approaches to neuroprotection are: presynaptic inhibition of excitatory amino-acid release, inhibition of upstream portions of the ischemic cascade and finally inhibition of more distal aspects of the ischemic cascade. Synergistic activity has been observed when these various approaches are combined. So far, none of the neuroprotective drugs evaluated in clinical trials have shown significant efficacy. The potential reasons for this lack of efficacy will be discussed and future approaches to increase the likelihood of success in clinical trials with neuroprotective drugs outlined. Specifically, diffusion-perfusion MRI can be used to identify patients with the most appropriate ischemic lesion for inclusion in a clinical trial and to eliminate patients not appropriate, i.e. lacunar stroke patients. Additionally, evidence is emerging that diffusion-perfusion MRI may be able to identify the existence and extent of the ischemic penumbra and therefore lead to clinical trials targeted at patients who are most likely to respond to treatment. The use of MRI to target patients who can still respond to therapy will help to extend the therapeutic time window. Another way to use neuroprotection, in combination with thrombolysis will be discussed. Neuroprotection may be useful with thrombolysis to provide another way to extend the time window for successful therapy and to ameliorate the consequences of secondary injury associated with reperfusion. Past experiences with neuroprotection have been disappointing for a variety of reasons, but hopefully the future will be brighter, if we learn from past mistakes and adopt new approaches such as those afforded by diffusion-perfusion MRI.

INVITED REVIEW

Growth Factors and Stem Cells in the Treatment of Cerebral Ischemia

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Stroke remains a major cause of morbidity and mortality in the US and worldwide. It causes deficits of motor, cognitive, language and visual function. Some degree of functional recovery occurs after stroke, although often incomplete. Such recovery is likely due to functional and structural reorganization of the remaining intact brain.

We have investigated the role of growth factors in animal models of focal cerebral infarction, especially basic fibroblast growth factor (bFGF), a factor that supports neuronal survival and axonal outgrowth, and osteogenic protein-1 (OP-1, BMP-7), a factor that supports dendritic outgrowth. The endogenous expression of both of these factors is increased in brain after focal stroke. Moreover, if recombinant bFGF is administered exogenously (intracerebrally or intravenously) within a few hours after the onset of ischemia, infarct size is reduced1,2, presumably due to protection of cells at the borders of infarcts. On the other hand, if bFGF or OP-1 is administered intracerebrally (intracisternally) at later times (> 24 hours) after stroke, infarct size is not reduced, but neurological recovery is enhanced2-8, presumably due to stimulation of new neuronal sprouting and synapse formation in the remaining intact brain.

Recently, we have tested the ability of transplanted neural stem cells (NSCs), obtained from the neonatal mouse brain, to enhance stroke recovery in the same animal model. NSCs were given intracisternally or directly into the peri-infarct striatum with and without simultaneous administration of bFGF intracisternally. Both bFGF alone and NSCs alone showed significant benefit compared to the control group. The best result was seen with the combination of NSCs and bFGF9. Intracisternally administered mouse NSCs had migrated to peri-infarct tissue and possibly differentiated into both neurons and glia. The combination of NSCs and bFGF may enhance sensorimotor recovery through stimulation of endogenous recovery mechanisms and/or establishment of new connections in the post-stroke brain. More recently, we have obtained similar result using human umbilical cord blood stem cells.

In summary, growth factors and stem cells have promise as treatments to enhance functional recovery after stroke.

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INVITED REVIEW

Beyond DWI
Novel MRI Sequences for Studying Ischemic Brain Injury

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Diffusion weighted imaging (DWI) has been widely used to study patients with acute ischemic stroke. While DWI is highly sensitive in depicting an acute ischemic lesion, its value in predicting final infarct volume has been called into question in the acute stage. However, when coupled with perfusion weighted imaging (PWI), a mismatch has been suggested to delineate reversible ischemic lesions that may be amenable to therapeutic interventions. A number of clinical trials of neuroprotective agents are ongoing in the US and other countries applying DWI/PWI in the selection of patients with salvageable brain tissue. However, the lack of quantitative measurements for the perfusion-weighted images, the definitions of the ischemic lesions are somewhat subjective, making it difficult to consistently determine the ischemic lesions. At the Washington University/Barnes-Jewish Hospital, the Stroke Management and Rehabilitation Team (SMART) has been applying a number of novel MR techniques to aid in the delineation of the dynamic pathophysiology of brain injury following ischemia. Novel MR sequences based on the BOLD mechanism are useful in the assessment of the extent of deoxygenation in ischemic tissue and adjacent areas to derive the oxygen extraction fraction (OEF). In addition, an absolute measurement of CBF was also obtained for each patient. By combining both MR measured CBF and OEF, $CMRO_2$ may also be estimated. Using this MR-$CMRO_2$ method, we noted significant difference between core lesions that went on to become infracted *vs* penumbra with viable brain tissues. Further advances in the development of MR-$CMRO_2$ may obviate the need of PET scanners to measure CBF, OEF, and $CMRO_2$, and may permit serial imaging to delineate the dynamic pathophysiology of brain ischemia. These MR-derived parameters may also supplement DWI/PWI in predicting the fate of acute ischemic lesions.

The visualization of water diffusion anisotropy in cerebral white matters has made diffusion tensor imaging (DTI) a promising tool for non-invasive *in vivo* neuronal fiber tract mapping. This technique has been applied in human and animal brains for neuronal fiber tracking in three dimensions. DTI may be used to assess the extent of myelin formation or degradation. It may also differentiate demyelination from the axonal injury. The DTI method has been used at the Mallinckrodt Institute of Radiology to assess myelin abnormalities in mice with genetic defects in myelination including twitcher, shiverer, AD and patients with multiple sclerosis and AD. We have also applied DTI to evaluate animal models of ischemic brain and traumatic spinal cord injury. DTI has greater sensitivity than conventional MR sequences in identifying acute or chronic white matter lesions, and is likely to be useful in the future to monitor the resolution or progression of white matter lesions caused by ischemia, trauma, or chronic neurodegenerative diseases.

INVITED ARTICLE

Co-Administration of Neural Stem Cells and Basic Fibroblast Growth Factor Enhances Functional Recovery after Focal Cerebral Ischemia in Rats

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In previous studies, we showed that intracisternal injection of basic fibroblast growth factor (bFGF) enhances the recovery of sensorimotor function of the contralateral limbs following focal stroke in rats1, 2. In the current studies, we tested the effect of bFGF (administered intracisternally) in combination with neural stem cells (NSCs), obtained from the neonatal mouse brain, administered intracisternally or directly into the peri-infarct striatum at 1 (or) and 3 days after the onset of the cerebral ischemia in rats.

Right cerebral infarcts were made in the dorsolateral cerebral cortex and underlying striatum by electrocoagulation of the proximal middle cerebral artery (MCA). The animals then received injections of (1) vehicle, (2) bFGF alone (0.5 μg), (3) NSCs alone (10^6) or (4) bFGF(0.5 μg) plus NSCs(10^6) at 1 (or) and 3 days after stroke. Behavioral tests were carried out for 21 to 45 days. Histology and immunohistochemical staining of brain tissue then followed. For the behavioral tests, we used limb placing tests to examine sensorimotor recovery, the cylinder test which monitors spontaneous forelimb use, the body swing test which shows side preferences, and the reaching test which measures reaching ability of the forelimbs. We found that, treatment with bFGF alone or NSCs alone enhanced recovery compared to the vehicle group. Among all the groups, the animals that received bFGF plus NSCs performed the best in all tests over time. Infarct volume analysis showed no difference among groups.

Immunohistochemistry showed engraffment of mouse donor cells in peri-infarct regions of rat brain. Some of these cells appeared to have differentiated into glial cells and perhaps neurons as well. The mechanism by which bFGF and NSCs enhances functional recovery in this model maybe due to new axonal growth in the intact contralateral hemisphere and/or newly generated glia and neurons.

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