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Review

The development of stroke therapeutics: Promising mechanisms and translational challenges

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ABSTRACT

Ischemic stroke is the second most common cause of death worldwide and a major cause of disability. Intravenous thrombolysis with rt-PA remains the only available acute therapy in patients who present within 3 h of stroke onset other than the recently approved mechanical MERCI device, substantiating the high unmet need in available stroke therapeutics. The development of successful therapeutic strategies remains challenging, as evidenced by the continued failures of new therapies in clinical trials. However, significant lessons have been learned and this knowledge is currently being incorporated into improved pre-clinical and clinical design. Furthermore, advancements in imaging technologies and continued progress in understanding biological pathways have established a prolonged presence of salvageable penumbral brain tissue and have begun to elucidate the natural repair response initiated by ischemic insult. We review important past and current approaches to drug development with an emphasis on implementing principles of translational research to achieve a rigorous conversion of knowledge from bench to bedside. We highlight current strategies to protect and repair brain tissue with the promise to provide longer therapeutic windows, preservation of multiple tissue compartments and improved clinical success.

1. Introduction to ischemic stroke

Stroke ranks second to ischemic heart disease as a cause of death and long-term disability with 4,000,000 new cases per year worldwide. The incidence is predicted to grow with the increasing age of the population (Donnan et al., 2008). Ischemic strokes constitute ~75–85% of all strokes while hemorrhagic strokes amount to ~15–20% of the acute stroke incidence. Stroke is a rapidly developing cerebrovascular event triggered by a thrombus or embolism in an extraparenchymal cerebral vessel (commonly in the middle and anterior cerebral arteries) and resulting in clinical symptoms of neurological impairment due to the interruption of blood flow to the brain. The biochemical cascade that evolves in response to injury includes initial energy failure, loss of ionic gradients and excitotoxicity, leading to a rapid death of neurons in the area adjacent to the blocked supply artery, termed the "core ischemic zone". Cells in the region surrounding the ischemic core, called the "penumbra", degenerate as a result of inflammatory stressors and apoptosis over a period of hours and days following the initial stroke insult. Without therapeutic intervention this penumbral area will die and become recruited into the core ischemic zone (Fisher, 2004; Fisher and Garcia, 1996). Neurons and other cells within the penumbra are salvageable and remain the target of most neuroprotective strategies; however they become increasingly "at risk" with the passing of time. This process is ultimately linked to the therapeutic treatment window in stroke that refers to the time interval post the onset of ischemia, within which any treatment must be given to avoid the progression of neuronal cell death (Baron and Moseley, 2000). With elapsing time, platelets and blood cells adhere to the endothelium of ischemic vessels and fibrin plugs the capillaries hindering reperfusion. This results in a "no reflow" phenomenon and the cessation of blood flow to distant brain areas even if the occluded parent vessel is ultimately recanalized.

There are two major classes of therapeutic approaches to acute ischemic stroke: neuroprotectants that target biochemical pathways controlling cellular fate to preserve brain function and/or enhance neuronal repair and recovery and thrombolytics that restore cerebral blood flow. A third approach using interventional devices designed to elicit reperfusion following surgical removal of an occluding thrombus, such as the MERCI retriever, is not discussed in this review (but see Smith et al., 2008).

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Despite the discovery of multiple agents effective in animal models of stroke (O'Collins et al., 2006), the completion of 129 phase II trials and 60 phase III stroke trials has resulted in few effective therapies (Suwanwela and Koroshetz, 2007). More than a decade since its approval, the thrombolytic recombinant tissue plasminogen activator (rt-PA, Genentech's Activase) remains the only approved therapeutic agent for acute ischemic stroke, other than the MERCI device for mechanical removal of embolus clot. However, the risk of hemorrhage (Wardlaw et al., 1997) and a restrictive 3-h treatment window reduces the pool of stroke patients eligible for rt-PA to only 5–8%. In selected countries (Japan and Spain), a free radical scavenger, Edaravone (Mitsubishi's Radicut) and Citicholine, a phosholipid supplement (Ferrer's Somazina), are approved as neuroprotectants. However, their efficacy is weak and limited by side effects. This lack of effective agents establishes a high unmet medical need and an opportunity for stroke therapeutic development. A summary of drugs in development for stroke is shown in Table 1.

2. Thrombolysis

2.1. The current gold standard

The rationale for administering a thrombolytic to a stroke patient is to achieve reperfusion by breaking up an occluding thrombus and reestablishing cerebral blood flow. Treatment of patients with rt-PA (0.9 mg/kg, with a maximum dose of 90 mg) within 3 h of the onset of acute ischemic stroke has been shown to improve recovery in two clinical phase III trials on the basis of which rt-PA gained approval in the United States and most of Europe (Schellinger et al., 2001). Recent results from ECASS III trial have extended the rt-PA window to 4.5 h (Hacke et al., 2008). The use and efficacy of rt-PA, however, is highly restricted due to numerous exclusion criteria that include the presence of hemorrhage and the localization and size of embolic occlusion, all of which require careful evaluation by computerized tomography. Recent results from phase II trials demonstrate that the efficacy of thrombolysis and potentially drug delivery can be augmented by applying ultrasound energy and gaseous microbubbles or lipid microspheres (Alexandrov et al., 2008). Attempts to expand the therapeutic treatment window for thrombolysis to 6 h have not yet been successful (Hacke et al., 1995; Ogawa et al., 2007).

Two global phase III trials with a new dosing regimen for Ancrod (Viprinex, ASP I and ASP II), a defibrinogenating enzyme derived from the purified venom of the Malayan pit viper, are now recruiting 1300 patients with a 6-h window from first symptoms. Ancrod, which had been previously unsuccessfully studied in 1900 patients, has a dual mechanism of action combining direct cleavage of fibrinogen into soluble fragments and indirect activation of the plasminogen-plasmin pathway.

Another strategy has been to combine rt-PA treatment with either an anti-platelet aggregation factor or a direct thrombin inhibitor. This dual approach was thought promising because it could theoretically accelerate clot dissolution. In small cohorts of patients, Abciximab, a glycoprotein IIb/IIIa inhibitor (platelet aggregation inhibitor) or Argatroban, a thrombin inhibitor, have been shown to improve recanalization following ischemia when administered with rt-PA in small cohorts of patients (Abciximab Emergent Stroke Treatment Trial, 2005). However, large phase III trials have been terminated for lack of efficacy and excessive bleeding.

3. Tissue protection

3.1. Advances from neuroimaging

Advances in magnetic resonance (MR) imaging such as diffusion/perfusion (DWI/PWI) mismatch (see later) have been used as surrogate markers for detecting and estimating the volume of

Table 1
Drugs in development for the treatment of stroke

Drug name	Probable mechanism of action	Company	Probable clinical phase
NXY-059 (Cerovive)	Free radical scavenger	AstraZeneca/Renovis	Phase III (recently terminated)
Vipriniex (ancrod)	Thrombolytic	Abbot/Knoll/Neurobiol.Technologies	Phase III (recently failed)[a]
Desomteplase	Thrombolytic	PAION/Forest/Shering AG	Phase III (recently failed)[a]
Citicholine	Neuroprotectant	Teva/Grupo Ferrer/Takeda	Phase II/III (recently failed)[a]
Albumin	Neuroprotectant	University of Miami/NIH	Phase III
DP-b99	Calcium chelator	D-Pharm	Phase II (Completed)
ONO-2506/MK-0724 (Proglia)	Neurotrophic glial modulator	Ono Pharm/Merck/Neurobiol. Tech.	Phase II (recently terminated)
Cafeinol	Caffeine + ethanol	University of Texas/InnerCool Technologies	Phase II
Piclozotan (SUN-N4057)	5-HT1A receptor agonist	Asubio	Phase II (recently terminated)
Encadin (NS-7)	Calcium channel blocker	Nippon Shinyaku	Phase II
Microplasmin	Thrombolytic	ThromboGenics	Phase II
S-18986	AMPA receptor modulator	Servier	Phase II
Msc-1 (AGY-94806)	Opioid receptor sigma agonist	AGY Therapeutics/M's Science	Phase II
BRX-345 (arimoclomol)	Heat shock protein inducer	CytRx	Phase II
AX200 (G-CSF)	Growth factor	Sygnis	Phase II
NTx-265	Stem cell stimulator (EPO receptor agonist)	Stem Cell Therapeutics	Phase II
MRX-801	SonoLysis + tPA	ImaRx Therapeutics	Phase II
Alfimeprase	Thrombolytic	Nuvelo	Phase II
LuAA24493	Carbamylated EPO	Lundbeck	Phase I
ONO-2231	PARP1 inhibitor	Ono Pharm	Phase I
Solulin (PN-02)	Neuroprotective thrombolytic	PAION/Bayer Schering Pharma AG	Phase I
Neu2000	NMDA antagonist/antioxidant	AmKor/Choongwae pharma	Phase I
AEOL-10150	Antioxidant	Aeolus Pharm	Phase I
BAY-387271	Cannabinoid agonist	Bayer	Phase I
HF-0220	Neuroprotective steroid	Hunter Fleming	Phase I
HF-0420	Heparinoid	Hunter Fleming	Phase I
MC-1	Vitamin B derivative	Medicure Inc	Phase I
SUN-N8075	Na^+/Ca^{2+} channel blocker	Daiichi Sankyo	Phase I
TS-011	Arachidonic acid modulator	Taisho Pharmaceuticals	Phase I
NA-1	PSD-95 inhibitor	Arbor-Vita/NoNO Inc	Phase I
ILS-920	Immunophilin ligand	Wyeth	Phase I

Source data obtained from http://www.clintrials.gov, http://www.trialtrove.com and http://www.datamonitor.com.
[a] Modified dosing regimens currently pursued in new trials.