Brain Repair after Stroke

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Main Points

Introduction

Therapies for brain repair

Principles of brain repair
Introduction

Therapies for brain repair

Principles of brain repair
Brain repair: a definition

Brain repair can be defined as a process---spontaneous or therapeutically induced---that restores some aspect of brain structure or function after an insult.

Not preventing or reversing or limiting the insult.

Rather: regrowth, repair, restoration, rewiring.
Despite tPA approval, disability is common after stroke.

Only 2-3% of US patients with acute ischemic stroke receive iv tPA (< 3 hr).

Approximately 1/2 of those who receive iv tPA have significant long-term disability.

Additional treatments are needed to reduce disability after stroke.
Introduction

Therapies for brain repair

Principles of brain repair
Potential human restorative therapies

- Growth factors (e.g., b-FGF, OP-1, G-CSF, Erythropoietin)
A two growth factor combination

Kolb et al, JCBFM 07
Placebo
EGF+EPO

Belayev et al, Brain Res 09
Placebo
β-hCG+EPO
β-hCG+EPO, started 24 hr after stroke onset, improve motor function after MCAo in rat.
BETAS
Beta-hCG and Erythropoietin Treatment of Acute Stroke

A 3 site, open label, non-controlled, phase IIa safety trial

n=15; started Rx 24-48 hr after stroke onset; 90 d follow-up

b-hCG IM d 1,3,5 of study; EPO IV d 7,8,9 of study

Mean baseline NIHSS score = 10

No safety concerns; 8/12 with d90 Barthel Index score 95-100

clinicaltrials.gov # NCT00362414
BETAS
Beta-hCG and Erythropoietin Treatment of Acute Stroke

Minimal effects on hemoglobin and reticulocyte count

Serum hemoglobin g/dL vs. Time post-stroke

Reticulocyte Count (%)
Now enrolling in

Randomized, double-blind, placebo controlled, dose escalation study of human chorionic Gonadotropin (hCG) and Erythropoietin alpha (EPO) in acute Ischemic Stroke patients study ("REGENESIS" Study)

clinicaltrials.gov # NCT00938314
Potential human restorative therapies

- **Growth factors** (eg b-FGF, OP-1, G-CSF, Erythropoietin)
- **Cell-based** (eg LBS neurons (NT2/D1 teratocarcinoma), marrow MNC, mesenchymal stromal cells, embryonic stem)
Marrow stromal cells

• MSC are pluripotent cells normally found in bone marrow
• MSC tend to hone to sites of tissue injury
• Though MSC can differentiate into bone, fat, liver, muscle, etc; in CNS, “inducible pharmacy on wheels”
• i.v. MSC improve neuro outcome in animals with stroke when treatment is started up to 30 days after stroke onset
• MSC safe in 321 human subjects to date, mostly cardiac
Phase contrast of human MSC culture

Early culture

Day 13 culture

Koc et al 2000

Tom Lane, UCSD SCPL
**Trial runs of UCI marrow aspirate in healthy controls**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Age (years)</td>
<td>56.4 ± 21.8 (range 21-82)</td>
</tr>
<tr>
<td>Gender</td>
<td>2M/6F</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.2 ± 1.0</td>
</tr>
<tr>
<td>Volume bone marrow aspirated (cc)</td>
<td>29 ± 2 (median 30)</td>
</tr>
<tr>
<td>Visual Analog Pain Scale score</td>
<td>2.4 ± 1.4 (range 0.9-5.1)</td>
</tr>
<tr>
<td>Post-processing MNC (x 10^6) / kg body weight</td>
<td>0.9 ± 1.0 (range 0.4 – 3.3, median 0.6)</td>
</tr>
<tr>
<td>Post-culture MSC (x 10^6) / kg body weight</td>
<td>1.4 ± 1.5 (range 0.6 – 5.0, median 1.0)</td>
</tr>
</tbody>
</table>

Data from 8 healthy subjects (marrow aspirated, but no cells transfused)
Potential human restorative therapies

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- **Cell-based** (eg LBS neurons (NT2/D1 teratocarcinoma), marrow MNC, mesenchymal stromal cells, embryonic stem)
- **Small molecules** (eg amphetamine, methylphenidate, levodopa, ropinirole, SSRIs, sildenafil, anti-NogoA Ab)
“A Randomized, Placebo-Controlled, Double-Blind Study of Ropinirole In Chronic Stroke”

Steven C. Cramer, Bruce H. Dobkin, Elizabeth A. Noser, Rachelle W. Rodriguez, Lori A. Enney

Stroke 2009
A Single-Blind Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Repeat Doses of GSK249320 in Patients With Ischemic Stroke

This study will enroll 48 subjects at 13 sites in US, Canada, and Germany

clinicaltrials.gov # NCT00833989
Potential human restorative therapies

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- **Small molecules** (eg amphetamine, methylphenidate, levodopa, ropinirole, fluoxetine, anti-NogoA Ab, sildenafil)
- **Intensive physiotherapy, other training**
EXCITE trial: a positive chronic treatment

222 patients; 1st stroke prior 3-9 months; moderate arm deficits
Prospective, single-blind, randomized, multisite U.S. trial
Randomized: usual care vs. 2 wks constraint induced therapy
Significant gains, still positive at 2 yrs

Wolf et al; JAMA 296:2096; Lancet Neurology 7:33
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- Intensive physiotherapy, other training
- Robotic, neuroprosthetic, other devices
Hand Wrist Assistive Rehab Device (HWARD)

Takahashi et al, Brain 2008
Potential human restorative therapies

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- **Intensive physiotherapy, other training**
- **Robotic, neuroprosthetic, other devices**
- **Electromagnetic stimulation of the brain**
- **Motor imagery, observation, other cognitive Rx**
Introduction

Principles of brain repair

Therapies for brain repair

3. ISN/S 2000 @ Seven Clear Learning
1. Brain repair is time sensitive

- **Acute**: spontaneous growth/repair
- **Subacute**: stable, remains therapeutically accessible

(Duncan et al Stroke 1992)
Advantages of initiating brain repair therapy early

- brain is biologically galvanized
- high patient access
- OT, PT, other therapy already ordered
- no learned disuse
2. Brain repair is experience-dependent

ChABC + task-specific rehab: markedly better manual dexterity
ChABC + no rehab: modest recovery in skilled reaching
Control + task-specific rehab: modest recovery in skilled reaching
ChABC + general rehab: worsened skilled reaching

García-Alías et al, Nat Neurosci 12:1145; 2009
2. Brain repair is experience-dependent

ChABC + task-specific rehab: markedly better manual dexterity

“Optimal recovery therefore requires a combination of ChABC-induced sprouting and rehabilitation to mold the new connections.” -- García-Alías et al

See also Adkins et al, Exp Neurol 212:14 [brain stim]; Hovda & Feeney, Brain Res 298:358 or Feeney et al, Science 217:855 [amphetamine]
2. Brain repair is experience-dependent

Experience includes Occupational Therapy, Physical Therapy, Speech Therapy, others

Experience influenced by rehab setting and length of stay

Standardizing post-stroke experience across subjects, sites, and countries, can therefore be difficult

At least: can measure these variables
2. Brain repair is experience-dependent

Table 2. Therapy Received by Patients Outside of the Study

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>No. of Subjects Receiving Any Outside Therapy During Study Participation in the Ropinirole + PT Group (n=17)</th>
<th>No. of Subjects Receiving Any Outside Therapy During Study Participation in the Placebo + PT Group (n=16)</th>
<th>P</th>
<th>Mean No. of Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational therapy</td>
<td>4</td>
<td>4</td>
<td>1.0</td>
<td>21</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>7</td>
<td>13</td>
<td>0.03</td>
<td>12</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>4</td>
<td>1</td>
<td>0.34</td>
<td>19</td>
</tr>
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In the Ropinirole study, placebo group got significantly more outside physical therapy than Ropinirole group.

Cramer et al, Stroke 2009
Many sources of variance affecting stroke outcome

| Pre-stroke disability genetics | Effects on brain function |
| Age | Acute stroke interventions |
| Handedness | Time post-stroke |
| Medical co-morbidities | Post-stroke depression |
| Initial and final deficits | Medications ( + and - ) |
| Injury mechanism, side, topography, volume | Caregiver, social factors |
| | Quantity, quality, and timing of post-stroke therapy |
### Many sources of variance affecting stroke outcome

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After stroke, many factors can affect outcome and restorative therapy effects.
When the therapeutic target is brain repair, can measures such as of injury, function, or genetics improve decision making for individual patients?
**Hypothesis:** Treatment “x” improves behavioral gains from neurorehabilitation

**Subhypothesis:** Gains maximized when a measure of CNS function guides prescription of treatment “x”

In coronary art dz, patient gains are maximized when a measure of heart function guides treatment (such as exercise treadmill or dobutamine echo)

- measure TSH to guide tx hypothyroidism
- measure EPS to guide tx cardiac arrhythmia
- measure PFT to guide tx COPD

Repairing the brain isn’t flu vaccination
Injury to corticospinal tracts predicts treatment gains

At baseline, the proportion of motor tract injured was better at predicting treatment response than was infarct volume, behavioral status, or demographics.
Injury predicts gains in a clinical study

Stinear et al, Brain 2007
“Functional potential in chronic stroke patients depends on corticospinal tract integrity”

17 pts, 29 mo post-stroke, mean NIHSS=4

Treatment-induced gains in arm motor function predicted by
(a) White matter integrity (MRI-DTI: PLIC FA asymmetry)
(b) Neurophysiology (motor evoked potential)
Injury predicts gains in a clinical study

Greater asymmetry of WM integrity in posterior limb of internal capsule

DTI identified subgroup according to injury, predicted Rx response

Stinear et al, Brain 2007
Function of motor cortex predicts gains in a clinical trial

Multivariate assessment

NOTE: age, time post-stroke, and infarct volume did not survive in model

Cramer et al, Stroke 2007
Function of motor cortex predicts gains in a clinical trial

Multivariate assessment

FMRI identified subgroup, predicted Rx response

Cramer et al, Stroke 2007
Genetics of motor cortex plasticity

FDI map area

Val/Val

Kleim et al, 2006; Nat Neurosci
val<sup>66</sup>met BDNF polymorphism associated with reduced short-term, activity-dependent motor cortex plasticity

Kleim et al, 2006; Nat Neurosci
Genetics predicts gains in a clinical study

Among 241 subjects in the GAIN trials, significantly (p<0.05)

• worse recovery at 1 mo with BDNF val/met or ApoE4 genotype

• lower % with minimal disability (Rankin = 0-1) at d90 with ApoE4
Genetics predicts gains in a clinical study

Among 241 subjects in the GAIN trials, significantly \( p<0.05 \)

- lower % with minimal disability \( (Rankin = 0-1) \) at d90 with ApoE4

- NINDS tPA trial; NEJM, 1995

Getting iv tPA instead of placebo: ARR = 13%

Getting ApoE4 (-) instead of ApoE4 (+): ARR = 17%

NINDS tPA trial; NEJM, 1995
4. Value of domain-specific endpoints

Different neurological domains recover to different extents.

Different neurological domains recover at different rates.

Restorative therapies might influence recovery of domains differently.

Cramer et al, Stroke. 2007;38:1393
4. Value of domain-specific endpoints

In BETAS, domain-specific endpoints provided greater insight compared to global outcome measures.

When d90 Barthel = 95
- patient CA-001 had arm motor Fugl-Meyer = 37 / 66
- patient BE002 had Boston Naming Test = 4 / 10
In BETAS, domain-specific endpoints provided finer resolution of specific deficits

--of 9 subjects with d90 NIHSS arm motor subscore = 0, Action Research Arm Test scores ranged from 48-57 (of 57)

--patient CA-002
NIHSS score with slight gains, baseline=8 to day 90=5
Arm motor Fugl-Meyer score with large gains, 14 to 53 (of 66)
Example of domain-specific endpoint

Trailmaking A testing in BETAS study

Baseline
Time=2 min
4 connected
2 errors

Day 6
Time=2 min
7 connected
1 error

Day 10
Time=2 min
24 connected
1 error
SPECIAL REPORT
MEDICINE & TECHNOLOGY: WHAT THE FUTURE MEANS FOR YOU
The Next Frontiers

Newsweek

FIXING YOUR BRAIN

BIONIC EYES & EARS
HIGH-TECH ALZHEIMER'S TREATMENTS
REWIRING DOCTORS

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