Clinical Study of Stereotactic Surgery for Drug Addiction

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Drug Addiction

Definition of WHO:

Compulsive and spontaneous drug-taking behavior which is characterized by non-medical usage, long and repeated exposure to addictive drugs and gradually increasing drug-taking dose.
Problem around the world

200,000,000 People Drug Abuse

10,000,000 People Lose Labor Ability

100,000 People Lose Lives
Types of Clinical Manifestations

- Physiological dependence
- Psychological dependence
After repeated drug exposure, a sudden withdrawal would cause series of withdrawal symptoms, which would made the abuser reinstated into drug-taking.

Dysphoria
Anxiety
insomnia
lachrymation
yawn
It means the **craving** for euphoria after withdrawal. It is the strong **desire** which drives the drug addicts to keeping their drug-taking behavior.
Effects of Conservative Therapies

- alleviating withdrawal symptoms (physiological dependence) → achieve detoxification
- hardly being helpful to craving (psychological dependence) → lead to relapse

Relapse rate after detoxification:
- Within one month: 90%
- Within six months: 97%

The drug abusers always fall into a vicious circle:

First use → Drug abuse → Detoxification → Relapse
Neuroanatomy of drug addiction

**Physiological dependence:**
- locus caeruleus (LC)
- periaqueductal gray matter (PAG)

**Psychological dependence:**
- nucleus accumbens (NAc)
- ventral tegmental area (VTA)
The mesolimbic dopamine system plays a central role in psychological dependence with the nucleus accumbens (NAc) serving as a key structure in mediating these effects. NAc is located where the head of the caudate and the anterior portion of the putamen meet just rostral to the anterior commissure, which belongs to the basal ganglia of the brain.
Neurophysiologic mechanism of psychological dependence

Brain reward system
Ablation of the NAc with minimally invasive stereotactic neurosurgery would lead to blockage of the mesocorticolimbic dopamine circuit, which would prevent craving for drugs after detoxification and in this way prevent relapse.
In 1998, we started preclinical and clinical exploration on the NAc surgery for drug addiction, after sufficient discussion with experts in ethics, neuroscience, neurosurgery, neurology, psychology and psychiatry.
From May 1999, we studied experiments on rats and rhesus by ablating nucleus related to addiction, such as NAc and ventral globus pallidus (VP) for choosing the candidate target for clinical application.
Conditioned place preference (CPP) experiment was employed as addiction model and the animals was trained with morphine. Different targets was ablated to see the influence to animals’ place preference.
# The influence of CPP after NAc and VP lesion

<table>
<thead>
<tr>
<th>groups (n=10)</th>
<th>white box</th>
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<tbody>
<tr>
<td><strong>Pre-operation</strong></td>
<td></td>
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<tr>
<td>NAc group</td>
<td>813.4±s30.1* #</td>
<td>86.6±s17.5</td>
</tr>
<tr>
<td>VP group</td>
<td>806.5±s27.4 △</td>
<td>93.5±s16.5</td>
</tr>
<tr>
<td>control</td>
<td>436.6±s21.7 *</td>
<td>463.4±s19.3</td>
</tr>
<tr>
<td><strong>Post-operation</strong></td>
<td></td>
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</tr>
<tr>
<td>NAc group</td>
<td>489.1±s21.3 #</td>
<td>410.9±s18.9</td>
</tr>
<tr>
<td>VP group</td>
<td>594.7±s30.2 ☆ △</td>
<td>305.3±s14.5</td>
</tr>
<tr>
<td>control</td>
<td>476.8±s19.6 ☆</td>
<td>423.2±s21.7</td>
</tr>
</tbody>
</table>

(* # △P<0.01 ☆ P< 0.05)
Animal experimental conclusion

- NAc is the main nucleus for modulating drug reinforcement
- Ablating the NAc could decrease drug-taking behavior of the addicted rats
With great relationship to drug psychological dependence

Inspired by the success of pallidotomy for Parkinson's disease

Study on NAc as a sole target could obtain more explicit results than that on multiple targets
1. Inclusion and exclusion criteria

(1) drug-taking history $\geq 3$y
(2) times of treatment before $\geq 3$
(3) informed consent process
(4) following physiological detoxification
(5) without contraindications
First case worldwide in July, 2000
272 cases was included
1 year non-relapse rate: 69.5%
Specific complications : 5.9%
Nucleus accumbens
Clinical Study for Alleviating Opiate Drug Psychological Dependence by a Method of Ablating the Nucleus accumbens with Stereotactic Surgery

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Key Words
Stereotactic surgery · Drug abstinence · Nucleus accumbens · Psychological dependence

Abstract
The aim of this study was to explore a new way of treating drug addiction by ablating the nucleus accumbens (NAc), which has a close relationship with drug-induced psychological dependence, using stereotactic surgery, blocking the mesocorticolimbic dopamine circuit, alleviating craving for drugs and lowering the relapse rate after detoxification. On the basis of animal experiments, stereotactic surgery was performed in 28 patients by making a lesion in the NAc bilaterally to treat opiate drug dependence. Indications, the criterion of therapeutic effect, treatment process and the therapeutic and safety evaluation index of the surgery were formulated particularly. The mean follow-up period was 15 months. Relapse has not occurred in 11 cases up till now. Drug-free time in these patients has been more than half a year in 4 cases (more than a year in 3 cases), and less than half a year in 7 cases. Relapse occurred in 15 cases after surgery. Drug-free time in these patients was more than half a year in 3 cases, between 1 month and half a year in 10 cases and less than 1 month in 2 cases. The therapeutic effect was excellent in 7 cases (26.9%), good in 10 cases (38.5%) and poor in
1. Conference of stereotactic and functional neurosurgery (USA, 2003.5)

2. Other four international conferences
After publication of our work, more than 10 hospitals carried out similar clinical studies in China. Most of the studies confirmed the therapeutic effect of NAc ablation for drug addiction but incurred doubt. A national survey on this treatment was performed in 2009, which was assigned and funded by Chinese Ministry of Science & Technology.
National Survey

1 year
Short term
Single center

5-year
Long term
Multi-center

Effectiveness
Safety

Department of Neurosurgery, Tangdu Hospital
& National Institute on Drug Dependence
Case file provided by 7 hospitals

Up to July, 2009  Total cases: 769 cases

Tangdu Hospital: 272 cases
Guangdong 999: 203 cases
Guangzhou 458: 185 cases
Sichuan Luzhou: 56 cases
Naval General Hospital: 32 cases
Shenyang 463: 10 cases
Shanghai Ruijing: 11 cases

Because of funds limit, a 150 cases sample investigation was carried on at last
Random select 150 patients from cases file

5 areas, appoint 1-2 hospitals as the center of follow-up study

Set up a healthy person group as control
The content of follow-up visit

Non-Relapse rate
Craving of drugs
Withdrawal syndrome

Complications
Craving of food, sex
Personality
Mental health
Life Quality
The result of urine test (-)

Image

The result of urine test (-)
Ride of ten thousands of kilometers
28 provinces
143 cities and districts
Telephone: 750 person-trips
Time consuming: 1.5 months
5-year Non-relapse rate: 50%
Efficacy

Craving for drug

- Preoperative (recall)
- Postoperative (recall)
- Now

Mean score

Non-relapse

Relapse
1. Long term efficacy (good)
2. Long term safety

- Surgical Group → Non-relapse Group
- Relapse Group
- Healthy Group

Low incidence of severe complications. Operation is safe!
Surgical treatment for addiction is one of the most important and effective method for drug addiction.

Comprehensive treatment is helpful.

- drug detoxification
- surgical treatment
- psychological rehabilitation
- return to society
3. International forum of minimal invasive neurosurgery, Beijing (2004.9)
5. Future of Neuromodulation Therapy in Clinical Neuroscience, seoul, Korea (2007.1)
7. 2010 CNS annual meeting, san francisco (2010.10)
8. The 8th AASSFN, Jeju, Korea(2011.6)
Top Ten Abstracts – Section on Stereotactic and Functional Neurosurgery

Moderators: Brian H. Kopell, Konstantin V. Slavin

1:30 – 1:39 PM
961
Treatment of Medically Intractable Mesial Temporal Epilepsy with Responsive Brain Stimulation: Results of a Subset Analysis from the RNS® System Pivotal Investigation

2:51 – 3:00 PM
970
Nucleus Accumbens Lesioning Appears to Reduce Opiate Dependence: Target Location Correlates with Outcome
Wang Xuellian, Paul S.A. Kalanithi, John Adler, Chang Chonggang, Ge Shunman, Li Nan, Gong Ning, Ma Jiubong, Wu Heming, Fang Wei, Gao Guodong

This research has been supported by several grants

In progress

Assigned program in the Eleventh Five-Year Plan of China----clinical study led by MHC
National Natural science foundation of China----basic research on DBS application to addiction
Shortage of ablation

- Hard to accepted ethically
  ---- irreversible injury
- Natural reward, character change?
- Ablation intensity is difficult to control
  ---- poor outcome if insufficient
  ---- more complication if severe
- Addiction can be cured but lesions are permanent
Prospect of DBS

- DBS is a possible better way
  - mimic the functional effect of lesion
  - non-invasive, reversible, adjustable

- Addiction is prevalent and similar to psychiatric disorders

- More acceptable ethically and draw great interest
NAc-DBS for Drug Addiction

2011-04-20 First Case
2011-11-08 second Case
Both are effective

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Thank You