Subdural Pharmacotherapy Device (SPD)
For epilepsy treatment

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Current Approach

Selective Therapy

Why drug delivery to CNS?

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Selective Therapy

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- Many patients with refractory epilepsy are not candidates for surgery, and are not helped by AEDs.
- It is estimated that about 200,000 patients in the U.S. are not candidates for currently available epilepsy surgery.
- There is still a large unmet need.
- Because it seems to work!!!!!!!
TRANSMENINGEAL PHARMACOTHERAPY

- regularly flushed subdural catheter
- seal
- electrode/sensor

BBB-bypassing drugs, delivered on demand by hybrid neuroprosthesis, with feedback from tissue

SYSTEMIC PHARMACOTHERAPY

- BBB-crossing drugs, delivered continuously by patient or physician, with no feedback from tissue

epileptogenic tissue

From: Ludvig et al.,
Epidurally delivered pentobarbital can terminate focal neocortical seizures in rats.

226 mM of PB
Suppression of focal neocortical EEG spiking in the seizure focus, in epilepsy patients

(From: Madhavan, Kuzniecky et al., 2008, Epilepsy Research)
Design of the first generation SPD, a “hybrid neuroprosthesis”, for the treatment of focal neocortical epilepsy affecting ~150,000 people in US (based on US Patent #6,497,699 to Ludvig and Kovacs in 2002)
Device hardware & software

(We consider the SPD developed if:
- it is fully implantable,
- it properly executes all minipump functions,
- it effectively transmits/receives data and instructions,
- it can be powered by a single battery for at least 4 years)
Subdural strip

Dual minipump

Microcontroller, side 1

Microcontroller, side 2

(From: Medveczky et al., in preparation for J. Neurosci. Meth.)
Frontal cortical subdural EEG recordings transmitted by the SPD RF module

- Anesthesia during surgery
- Moving around during memory task
- Ketamine sedation for minipump refilling
- Quiet wakefulness in home-cage
- Effect of subdural (ipsilat.) Ach delivery

Ipsilateral

Contra-lateral

420 μV
sec

Chewing artifacts

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Antiepileptic efficacy

- it is able to completely prevent the occurrence of focal neocortical seizures,
- and it can maintain this efficacy for long periods without the induction of tolerance)
Basic properties of the muscimol solution delivered with the SPD

Amanita Muscaria — GABA A agonist
Termination of Ach-induced frontal cortical EEG seizures by 1.0 mM muscimol delivered via the SPD in a bonnet macaque
Long-term periodic muscimol delivery into the primate frontal cortex via the SPD prevents focal seizures.
$^3$H-muscimol autoradiography with thionin counterstaining: coronal section from the brain of a rat subjected to epidural $^3$H-muscimol exposure for 1 hour

(Histology/autoradiography made at NeuroScience Associates, by Dr. Robert Switzer)
Device safety

SPD safety can be quantified if its long-term use is not accompanied with:
- neurological symptoms
- cognitive, emotional and motivational impairment
- abnormal neocortical EEG and cell firing patterns
- systemic side effects
- infection)
Monkey behavioral testing apparatus, suitable for assessing motor, cognitive and motivational functions.
Acquisition of spatial memory tasks by macaque monkeys before SPD implantation

(Test described in: Ludvig et al., 2003; Behav. Brain Res.)
Acquisition of a new spatial memory task by macaque monkeys during long-term (12-h interval) muscimol delivery with the SPD
EEG effects of subdural Ach and muscimol applications with the SPD; local and systemic concentrations of the applied muscimol

(HPLC assay made at Stanford Research Institute by Dr. Jacqueline Vazquez-DeRose)
Conclusions

In its present state, the muscimol-delivering SPD implant can prevent focal neocortical seizures in primates for many months without apparent side-effects or tolerance.

Animals tolerate the device and drug without major problems.

Many Challenges remain ahead:

Engineering
Safety in humans
What is this?
## Key team members in 2011

**Neuroscience studies:**
- Nandor Ludvig, M.D., Ph.D. (Program Director)
- Hai M. Tang, M.D. (animal experiments)
- Shirn L. Baptiste, B.S. (animal experiments)
- Carol Novotney, D.V.M. (veterinary consultation at SUNY)
- Jacqueline Vazquez-DeRose, Ph.D. (HPLC at Stanford Res. Inst.)
- Robert Switzer, Ph.D. (autoradiography at NeuroScience Assoc.)

**Engineering studies:**
- Geza Medveczky, M.S. (hardware and software at NYU)
- H. Jonathan Chao, Ph.D. (hardware at NYU Poly)
- N. Sertac Artan, Ph.D. (hardware and software at NYU Poly)
- Sandor Toth, M.S. (hardware and software)

**Clinical studies:**
- Ruben I. Kuzniecky, M.D. (epileptology)
- Orrin Devinsky, M.D. (epileptology)
- Jacqueline A. French, M.D. (epileptology)
- Chad Carlson, M.D. (epileptology)

**Neurosurgery studies:**
- Werner K. Doyle, M.D. (implantation)
- John G. Kral, M.D., Ph.D., (general surgery consultation at SUNY)

**Industrial partners:**
- Cygnus (control unit manufacturing)
- DocXS Biomedical (subdural strip manufacturing)