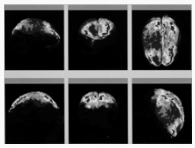
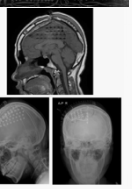
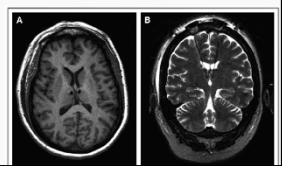
Epilepsy surgery Future treatment









Atthaporn Boongird,MD.

"Hippocrates, speaking generally, says, where medicine fails, steel may cure, where steel fails, fire may cure: where fire fails, the disease is incurable."

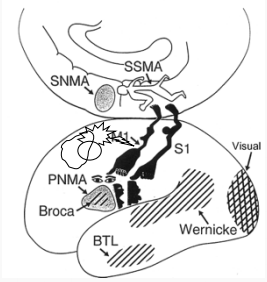
Cooke, History and method of cure of the various species of epilepsy, 1823

Future of Epilepsy surgery

- Method (s) of define epileptogenic zone
- New techniques for pre-surgical evaluation
- Outcome of MRI negative case will be improved.
- When EZ is not safely resectable, other novel treatments should be considered.

Concept of epilepsy surgery

- aim to get rid of ***epileptogenic zone*** without any neurological deficit.



— Symptomatogenic zone.
— Epileptogenic lesion
— Irritative zone

Functional deficit zone ??
- eg. Todd' s paralysis

LÜDER 2001

Different concept of "epileptogenic zone"

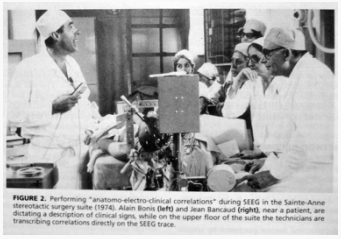
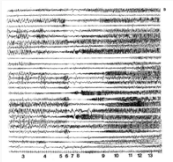


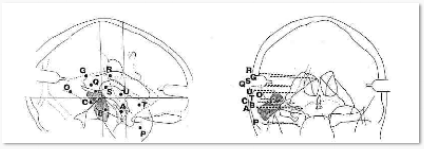
FIGURE 2. Performing "anatomo-electro-clinical correlations" during SEEG in the Sainte-Anne stereotactic surgery suite (1974). Alain Bonis (left) and Jean Bancaud (right), near a patient, are dictating a description of clinical signs, while on the upper floor of the suite the technicians are transcribing correlations directly on the SEEG trace.

"Different concept led to different surgical point of views and outcomes"

Stereoelectroencephalography,SEEG

Dr.ClaudioMunari (1943-1999)



Definition and localization of the epileptogenic zone

Epileptic Disord 2006; 8 (Suppl. 2): S16-26

The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis

Philippe Kahane[1,5], Elisabeth Landré[2], Lorella Minotti[1], Stefano Francione[3], Philippe Ryvlin[4,5]

The epileptogenic zone is the "site of the beginning of the epileptic seizures **and of their primary organization"**

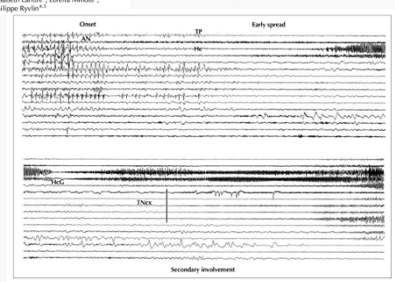


Figure 3. The Bancaud and Talairach definition of the epileptogenic zone includes the ictal onset zone (Amygdala, HA) and the zone of early spread (hippocampus, Hc; temporal pole, TP; parahippocampal gyrus, HCG). The temporal neocortex (TNcx) is only secondarily involved.

Non-invasive alternatives to the Wada test in the presurgical evaluation of language and memory functions in epilepsy patients

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Received December 4, 2006; Accepted March 26, 2007

ABSTRACT – The cognitive outcome of the surgical removal of an epileptic focus depends on the assessment of the localisation and functional capacity of language and memory areas which need to be spared by the neurosurgeon. Traditionally, presurgical evaluation of epileptic patients has been achieved by means of the intracarotid amobarbital test assisted by neuropsychological measures. However, the advent of neuroimaging techniques has provided new ways of assessing these functions by means of non-invasive or minimally invasive methods, such as anatomical and functional magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, transcranial magnetic stimulation, functional transcranial Doppler monitoring, magnetoencephalography and near infrared spectroscopy. This paper aims at comparing and evaluating the traditional and recent preoperative approaches from a neuropsychological perspective.

Key words: epilepsy surgery, neuroimaging technique, intracarotid amobarbital test, language, memory

Epileptic Disord 2007; 9 (2): 111-26

Table 1. Comparison of various techniques used in the presurgical exploration of language and memory functions in epilepsy patients.

Technique	Procedure	Expressive language	Receptive language	Memory assessment	Advantages	Disadvantages
IAT	deactivation by anesthesia	yes	yes	yes	direct measure, possibility to assess unilateral functions	invasive, uncomfortable, risk of morbidity, no localization, less suitable for young and mentally-challenged individuals
icESM	electrical stimulation	yes	yes	yes	direct measure, precise localization	invasive, requires patient's cooperation and surgical team expertise
Neuropsy. assessment	behavioural testing with standardized test batteries	yes	yes	yes	non-invasive, affordable, applicable to children and adults of all ages	no localization
Tachistoscopy	determination of visual field advantage	yes	yes	no	non-invasive, affordable, portable	no localization
Dichotic listening	determination of ear advantage	yes	yes	no	non-invasive, affordable, portable	no localization, requires patient's attention
MRI	structural assessment	no	no	yes (inference)	non-invasive, requires minimal cooperation, good spatial resolution	expensive, limited to structural abnormalities
fMRI	hemodynamic response to activation	yes	yes	yes	non-invasive, good localization and spatial resolution	expensive, requires patient's cooperation, less suitable for young and mentally-challenged individuals
PET	hemodynamic response to activation	yes	yes	yes (inference)	provides asymmetry in hypometabolism	expensive, a invasive, poor spatial and temporal resolution
SPECT	hemodynamic response to activation	yes	no	no	affordable	a invasive, poor spatial and temporal resolution
rTMS	deactivation by electrical interference	yes	no	no	non-invasive, direct measure, affordable	no reliable results within individuals and across centers
MEG	magnetic flux directly associated with activation	no	yes	no	non-invasive, direct measure, good temporal resolution	expensive, poor spatial resolution, limited with regard to depth of penetration, requires patient's cooperation
NIRS	hemodynamic response to activation	yes	yes	no	non-invasive, affordable, equipment portable, easily used in children	data acquisition limited to cortical surface, requires patient's cooperation
fTCD	hemodynamic response to activation	yes	yes	no	not-invasive, inexpensive, good temporal resolution, easily used in children	poor spatial resolution, no localization

Review article

Epileptic Disord 2013; 15 (2): 105-13

Outcome after epilepsy surgery in children with MRI-negative non-idiopathic focal epilepsies

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Received March 03, 2013; Accepted April 05, 2013

ABSTRACT – MRI is one of the most important diagnostic tools in the presurgical evaluation of patients suffering from pharmaco-refractory focal epilepsies. Presence of a lesion on MRI influences both diagnostic classification as well as selection for surgery; however, the implications for MRI-negative cases are far from well defined for such patients. Detection of potentially epileptogenic lesions depends on the techniques applied (high-field MRI, post-processing, etc.) and the experience of the neuroradiologist. The proportion of MRI-negative patients in reported epilepsy surgery cohorts ranges from 16 to 47%. Most MRI-negative patients undergo invasive long-term EEG recordings before a final decision regarding resection is possible. Post-operative seizure freedom rates, with few exceptions, range from 40 to 50%. Selection of surgical candidates and post-operative outcomes may be improved by recent developments in structural and functional imaging techniques and multimodal approaches. This report gives an overview of outcomes after epilepsy surgery in MR-negative patients with a focus on children. Issues regarding definitions, the role of established and recently introduced diagnostic tools, and the question of how outcome might be improved in the future are discussed.

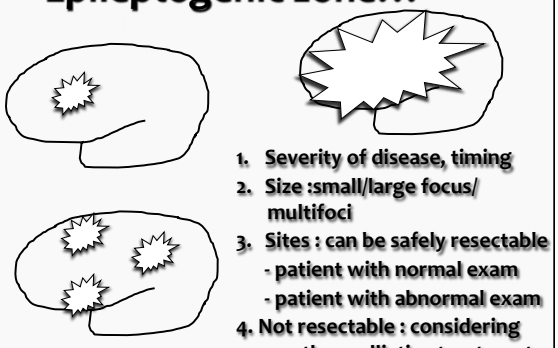
Key words: epilepsy surgery, childhood, outcome, cryptogenic, MRI, functional imaging

Table 1. Seizure outcomes in MR- patients.

Authors	Year of publication	Cohort	Aim of study	N	Period of recruitment	Follow-up (years)	Seizure-free outcome (%)	Outcome: Engel class I (%)	Outcome: Other (%)
Téllez-Zenteno et al.	2010	C+A	Meta-analysis for comparing MR+ and MR-	398	1995-2007	≥1	45		
		C		93			45		
Bell et al.	2009	C+A	Outcome MR- TLE	40	1997-2005	≥1	60		
Bien et al.	2009	C+A	Outcome MR+ and MR-	29	2000-2006	≥0.5	38	45	
Chapman et al.	2005	C+A	Outcome MR-	24	1994-2001	≥1	37	45	
Cukiert et al.	2001	C+A	Outcome and iEEG in MR-diffuse MRI	10	1997-2000	≥1	90		
Dorward et al.	2011	C	Outcome in MR- ETLE	22	1994-2007	≥2		36	
Jayakar et al.	2008	C+(A)	Outcome MR-	102	?	≥2	44		
Knosk et al.	2009	C+(A)	FCD study	26	1986-2006	≥2		54	
Lee et al.	2005	C+A	Outcome MR-	89	1995-2002	≥2	47		
McGonigal et al.	2007	C+A	iEEG	20	2000-2006	1	55		
Park et al.	2002	C+A	iEEG	18	1995-2000	≥1			44 (>90% seizure reduction)
RamachandranNair et al.	2007	C	Functional imaging	22	1998-2005	≥0.75	36		77 (<Engel IIIa)
Schneider et al.	2012	C+A	Functional imaging	18	2008-2010	≥2	56		
Seo et al.	2011	C	Functional imaging	25	2006-2009	≥1	48		
Siegel et al.	2001	A	MR- outcome	24	1992-1999	≥2		83	
Thivard et al.	2011	A	(Functional) imaging	32	2003-2006	NR		67	
Wetjen et al.	2009	C+A	iEEG and MR- outcome	28	1992-2002	>1	36	50	
Wu et al.	2013	A	Functional imaging	18	1990-2009	≥1	22		55 (Engel I+II)
Zhang et al.	2011	C+A	Functional imaging	20	2006-2009	≥1	35		

N: number of patients; C: children; A: adults; (A): young adults; iEEG: invasive long-term EEG recording; NR: not reported.

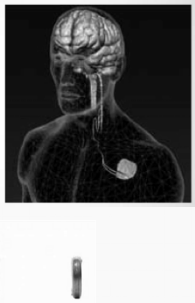
Epileptogenic zone???

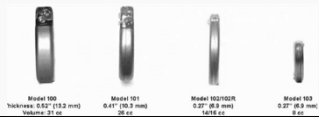


1. **Severity of disease, timing**
2. **Size :small/large focus/ multifoci**
3. **Sites : can be safely resectable**
   - **patient with normal exam**
   - **patient with abnormal exam**
4. **Not resectable : considering another palliative treatment**

Vagus Nerve Stimulation

- Advantages:
  - FDA approved since 1997
  - Low risk surgery
  - Possible Mood Benefits
- Disadvantages:
  - Mild to moderate impact on seizures
  - Vocal side effects
  - No significant control over device





Indication

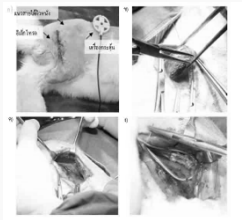
- The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications.
- Generalized onset seizures have been treated with VNS in Europe but are not FDA approved.

VNS

- Outcomes:
  - Reduction in seizure frequency, duration, spread.
    - EO3 and EO5 studies demonstrated 23-31% of patients had >50% reduction in seizure number. (at 3months)
    - Rate of seizure reduction may increase with stimulation out to 1 year and beyond with up to 61% of patients responding.
    - Patients report improved Quality of Life.
  - Improved interictal level of consciousness
  - Moderate chance of medication reduction

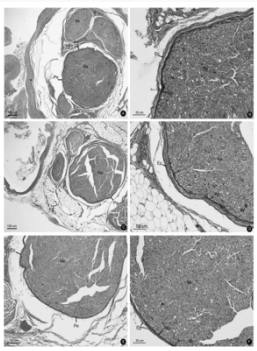
VNS (first prototype)

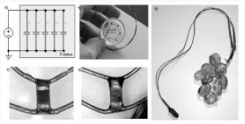
Rechargeable



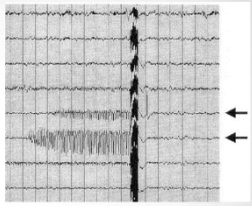
Sciatic nerve implant

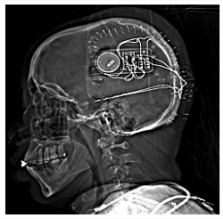
Invitro and invivo testing



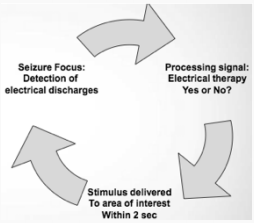


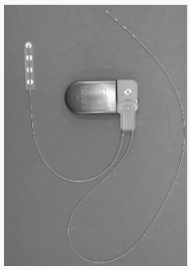
RESPONSIVE BRAIN STIMULATION NEUROPACE SYSTEM





CLOSED LOOP

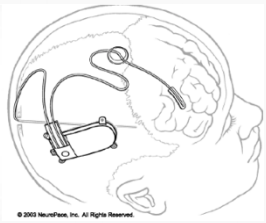




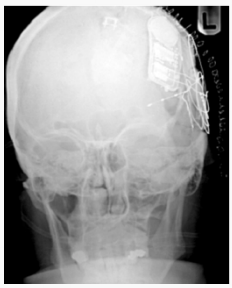
NEUROPACE

Preliminary results:

- Multi-center trial of 191 patients at 31 sites
- In 3 month blinded phase patients had 29% average reduction in sz.
- At 1 year 47% had >50% reduction in seizure frequency.
- Minimal adverse events.



NEUROPACE



NEUROPACE

- Advantages:
  - Addresses non-resectable, focal seizure disorder.
  - Open ended architecture. Therapy may improve as algorithms get smarter.
  - Minimized stimulation allows long battery life and may minimize stimulation side effects.
- Disadvantages:
  - Major surgery needed for implant
  - Risks similar to DBS surgery
  - Final study results and FDA approval pending.

ANTERIOR THALAMIC DBS

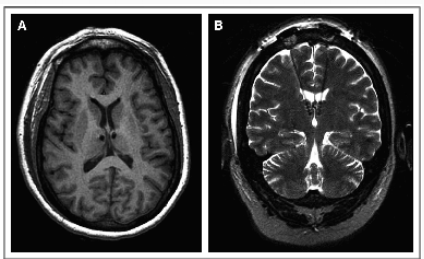


FIGURE 2. A, axial T1 and B, coronal T2-weighted magnetic resonance images depicting bilateral AN-DBS electrodes. AN, anterior thalamic nucleus; DBS, deep-brain stimulation.

Anterior thalamic nucleus DBS

- Outcomes: SANTE Trial
  - 110 patients randomized, double-blind design.
  - 60% of treated patients had >50% seizure reduction in first 3 months.
  - By 3 years patients had 68% average seizure reduction.
  - At 1 year 9% were seizure free
  - 44.5% had prior VNS, 24.5% had prior surgery

Deep Brain Stimulation

- Advantages:
  - Moderately better outcomes than VNS.
  - More targeted control at seizure spread
  - Known surgical technique
  - No vocal hoarseness
- Disadvantages:
  - Complications rare but potentially more severe than VNS
  - Open Loop design

NEUROSTIMULATION STUDY

TABLE 1. Controlled Studies Using Neurostimulation Techniques to Treat Epilepsy[a]

Target	Authors (Year)	Study Protocol (Duration)	No. of Patients	Outcome
Cerebellum	Van Buren (1978)[14]	Double-blind crossover (6-19 mo)	5	No improvement
	Wright (1984)[164]	Double-blind crossover (6 mo)	12	No improvement
	Velasco (2005)[144]	Double-blind crossover (24 mo)	5	>50% seizure reduction in 80% of patients
CM	Fisher (1992)[13]	Double-blind crossover (9 mo)	7	>50% seizure reduction in 3 of 6 patients in the open-label phase
	Velasco (2000)[97]	Double-blind crossover (minimum of 12 mo)	13	>50% seizure reduction in 90% of patients
AN	Fisher (2010)[166]	Double-blind, randomized (minimum of 13 mo)	110	40.4% median seizure reduction
Hippocampus	Tellez-Zenteno (2006)[7]	Double-blind crossover (6 mo)	4	15% seizure reduction
	Velasco (2001)[18]	Double-blind crossover (minimum of 18 mo)	9	>50% seizure reduction in all patients
	McLachlan (2009)[99]	Double-blind crossover (9 mo)	2	33% seizure reduction
VNS	The Vagus Nerve Stimulation Group (1995)[202]	Multicenter double-blind parallel group design (high vs low frequency)(14 wk)	114	≥50% seizure reduction in 31% of patients who received high-frequency stimulation
	Handforth (1998)[70]	Multicenter double-blind parallel group (3 mo)	196	28% seizure reduction in high-frequency stimulation group
	DeGiorgio (2000)[34]	Multicenter double-blind (12 mo)	195	>50% seizure reduction in 35% of patients
rTMS	Tergau (2002)[212]	Double-blind crossover (27 wk)	9	38% seizure reduction in 0.33 Hz frequency group
	Theodore (2002)[214]	Double-blind placebo-controlled (1 wk of active stimulation sessions)	24	No significant effect statistically
	Cantello (2007)[23]	Double-blind placebo-controlled (5 d of stimulation sessions)	43	No significant effect statistically
	Fregni (2006)[216]	Double-blind placebo-controlled in patient with cortical malformation (5 d consecutive sessions)	21	72% seizure reduction at 2 wk after rTMS and 58% at week 8 post-rTMS

[a] AN, anterior thalamic nucleus; CM, centromedian thalamic nucleus; rTMS, repetitive transcranial magnetic stimulation; VNS, vagal nerve stimulation.

Comparison of seizure control outcomes and the safety of vagus nerve, thalamic deep brain, and responsive neurostimulation: evidence from randomized controlled trials

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Departments of [1]Neurological Surgery and [2]Neurology, University of California at San Francisco, California

TABLE 1: Randomized controlled trials of VNS compared with other stimulation-based therapies*

Study	No. Patients (no. in active group)	% w/ Seizure Reduction, Blinded (95% CI)	% w/ Seizure Reduction, 1 Yr	% Responder Rate, Blinded	% Responder Rate, 1 Yr	Regulatory Approval: FDA	Regulatory Approval: CE Mark
VNS						yes	yes
EO3	114 (54)	24.5 (14.1–34.9)	43	31			
EO5	196 (94)	27.9 (21.0–34.8)	45	23.4	35		
thalamic DBS—SANTE	109 (54)	40.4 (NR)	41	NR	43	†	yes
cortical stimulation—RNS	191 (97)	37.9 (27.7–46.7)	NR	29	43	†	†

* Seizure reduction is defined as change in actively treated patients compared with their baseline seizure frequency. Responder rates are defined as a ≥ 50% reduction in seizure frequency experienced in actively treated patients. The ≥ 50% responder rate is not reported in the SANTE trial, although it was not significantly different from the untreated group. NR = not reported.
† Pending review.

Neurosurg Focus 32 (3):E14, 2012

TABLE 2: Adverse events across trials*

Adverse Event	VNS: EO3	VNS: EO5	Thalamic DBS (SANTE)	Cortical Stimulation (RNS)
hoarseness/voice change	37.2	66.3	—	—
coughing	7.4	45.3	—	—
nasopharyngitis	11.1	34.7	1.9	—
pain	5.6	28.4	—	0.5
dyspnea	5.6	25.3	—	—
headache	1.8	24.2	3.7	2.6
paresthesia	5.6	17.9	9.3	0.5
dyspepsia	—	17.9	—	—
vomiting	—	17.9	—	—
depression	—	—	14.8	1.1
nausea	—	14.7	—	—
memory impairment	—	—	13.0	0.5
injury (accidental)	—	12.6	1.9	—
fever	—	11.6	—	—
infection	—	11.6	—	—
anxiety	—	—	9.3	—
partial seizures w/ generalization†	—	—	9.3	—
complex partial seizures†	—	—	9.3	4.3
confusional state	—	—	7.4	—
influenza	—	—	5.6	—
simple partial seizures†	—	—	5.6	2.2
anticonvulsant toxicity	—	—	5.6	—
dizziness	—	—	5.6	—

* All reported adverse events occurring in ≥ 2.5% of patients during the blinded evaluation period. — = data not provided.
† New, increased, or exacerbated.

Nanotechnology for the Delivery of Drugs to the Brain for Epilepsy

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Abstract

Epilepsy results from aberrant electrical activity that can affect either a focal area or the entire brain. In treating epilepsy with drugs, the aim is to decrease seizure frequency and severity while minimizing toxicity to the brain and other tissues. Antiepileptic drugs (AEDs) are usually administered by oral and intravenous (IV) routes, but these drug treatments are not always effective. Drug access to the brain is severely limited by a number of biological factors, particularly the blood-brain barrier (BBB), which impedes the ability of AEDs to enter and remain in the brain. To improve the efficacy of AEDs, new drug delivery strategies are being developed; these methods fall into the three main categories: drug modification, BBB modification, and direct drug delivery. Recently, all three methods have been improved through the use of drug-loaded nanoparticles.

Neurotherapeutics. 2009 April

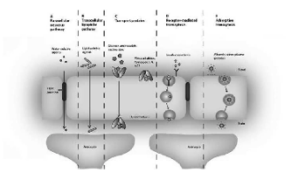

Figure 1.
Schematic of the BBB illustrating the various routes of molecular transport across brain capillary endothelial cells. A) Water-soluble agents can travel between the endothelial cells via tight junctions, but passage is highly restricted. B) In contrast, lipid-soluble agents easily penetrate the BBB by diffusing across the endothelial cell membranes. C) Carrier proteins present in the membrane facilitate crossing of substances such as monosaccharides, amino acids, peptides, nucleosides, choline, and organic cations. AZT = azidothymidine. D) Receptors specific for transferrin, insulin, insulin-like growth factor, lipoproteins, and leptin are also exposed on the surface of the endothelium to aid in penetration via transcytosis. E) Positively charged molecules can traverse the BBB through adsorptive transcytosis. These pathways can be exploited to enhance the entrance and accumulation of AED's into the brain parenchyma. Adapted by permission from Macmillan Publishers Ltd: Abbott JN, Romnback J, Hanssen E. Astrocyte-endothelial interactions at the blood-brain barrier. Nature Reviews Neuroscience 2006;7:41-53.

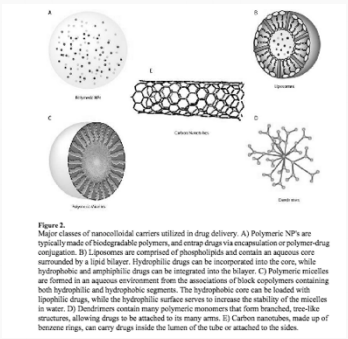

Figure 2.
Major classes of nanocolloidal carriers utilized in drug delivery. A) Polymeric NP's are typically made of biodegradable polymers, and entrap drugs via encapsulation or polymer-drug conjugation. B) Liposomes are comprised of phospholipids and contain an aqueous core surrounded by a lipid bilayer. Hydrophilic drugs can be incorporated into the core, while hydrophobic and amphiphilic drugs can be integrated into the bilayer. C) Polymeric micelles are formed in an aqueous environment from the associations of block copolymers containing both hydrophilic and hydrophobic segments. The hydrophobic core can be loaded with lipophilic drugs, while the hydrophilic surface serves to increase the stability of the micelles in water. D) Dendrimers contain many polymeric monomers that form branched, tree-like structures, allowing drugs to be attached to its many arms. E) Carbon nanotubes, made up of benzene rings, can carry drugs inside the lumen of the tube or attached to the sides.

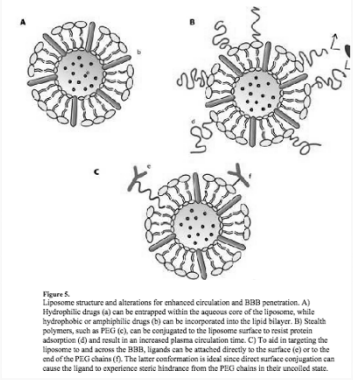

Figure 5.
Liposome structure and alterations for enhanced circulation and BBB penetration. A) Hydrophilic drugs (a) can be entrapped within the aqueous core of the liposome, while hydrophobic or amphiphilic drugs (b) can be incorporated into the lipid bilayer. B) Stealth polymers, such as PEG (c), can be conjugated to the liposome surface to resist protein adsorption (d) and result in an increased plasma circulation time. C) To aid in targeting the liposome to and across the BBB, ligands can be attached directly to the surface (e) or to the end of the PEG chains (f). The latter conformation is ideal since direct surface conjugation can cause the ligand to experience steric hindrance from the PEG chains in their uncoiled state.

Original Research

Epidural Pentobarbital Delivery Can Prevent Locally Induced Neocortical Seizures in Rats: The Prospect of Transmeningeal Pharmacotherapy for Intractable Focal Epilepsy

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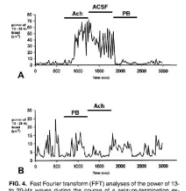

FIG. 4. Fast Fourier transform (FFT) analyses of the power of 13- to 20-Hz waves during the course of a seizure-termination experiment (A) and a seizure-prevention experiment (B). Horizontal axis, recording session time; vertical axis, power of the selected frequency band. Drug-exposure periods are as indicated. Note in (A) the clear power increase during acetylcholine (Ach) exposure and that this power increase is maintained, albeit at a slightly lesser degree, after the replacement of the epileptogenic compound with aCSF. The power of 13- to 20-Hz waves promptly returns to normal after pentobarbital (PB) delivery. As (B) illustrates, the Ach-related marked power increase is completely prevented by prior PB administration.

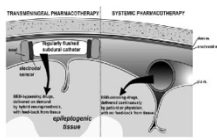

FIG. 6. Schematic diagram illustrating the principal characteristics of systemic and transmeningeal pharmacotherapies. In contrast to the traditional systemic (e.g., oral) pharmacotherapeutic approach, transmeningeal pharmacotherapy offers drug deliveries directly and exclusively to the epileptogenic brain tissue, via sealed, single or multiple, regularly flushed, subdural/epidural catheter units equipped with recording electrodes/sensors that provide feedback from the exposed neural tissue.

Epilepsia, Vol. 47, No. 11, 2006

" Hippocrates, speaking generally, says, where medicine fails, steel may cure, where steel fails, fire may cure: where fire fails, the disease is incurable."

Cooke, History and method of cure of the various species of epilepsy, 1823

Where steel fails, fire may cure: where fire fails, the disease is truly incurable, but we can possibly modulate it by the emerging novel treatment(s)

Thank you