Outcome Scale measured at 6 months from the time of injury (Figure).

A favorable outcome was determined by stratifying patients according to the severity of their initial injury so that patients with a less severe initial injury had to have a better recovery than those with a more severe injury to have a favorable outcome. A total of 882 patients were randomized between April 2010 and October 2013. The progesterone and placebo groups were balanced in terms of demographics and injury severity; 53.5% of patients had an initial GCS score of 5 to 8, with the remainder divided between a GCS score of 4 (severe injury) and a GCS score of 9 to 12 (moderate injury). Favorable outcomes were achieved in 51.0% of progesterone-treated patients and 55.5% of placebo patients. A secondary analysis in which a favorable outcome was simply considered to be an Extended Glasgow Outcome Scale score $\geq 5$ (equating to moderate disability or better) provided similar results. There was also no significant difference in mortality between the 2 groups. Additionally, adverse events were similar between the groups with the exception of phlebitis and thrombophlebitis (considered a serious adverse event) occurring significantly more often in the progesterone group. Thus, although progesterone maintains a good safety profile, it does not appear to have an effect on functional outcome when administered to patients with acute TBI.

Despite data from multiple animal studies, 2 human trials preceding it, and a high-quality study design, the PROTECT III trial was not able to establish a role for progesterone in the treatment of TBI. The authors cite the heterogeneity of injuries, patient pre-existing conditions, and the characteristics of individual patients as potential confounding factors. Although these negative results are disappointing, the study paves the way for the investigation of future compounds.

**REFERENCE**


**Closed-Loop Deep Brain Stimulation Successfully Modulates Hippocampal Activity in an Animal Model**

Recent research in brain stimulation techniques (in the context of a variety of neurological conditions, including movement disorders, psychiatric disorders, and epilepsy) has turned toward understanding the
induced effects of stimulation at a systems level. These efforts often involve stimulating one region of the brain and examining the response characteristics of another. In this vein, Stypulkowski et al. recently published a study of hippocampal excitability and its changes in the context of both local hippocampal and remote electric stimulation of the anterior thalamus. The authors demonstrate that broadband local field potential (LFP) suppression can be produced in the hippocampus via either direct hippocampal or thalamic stimulation and that these effects are dependent on the stimulation parameters used. Additionally, the authors developed and demonstrated 2 closed-loop stimulation schemes in which stimulation therapy was selectively delivered and modulated on the basis of real-time feedback in the form of hippocampal theta band activity.

The authors performed these studies in a sheep model (n = 3) with Medtronic model 3387 deep brain stimulation leads stereotactically placed in the hippocampus and model 3389 deep brain stimulation leads placed in the anterior thalamus unilaterally. Long-term implant durations ranged from 24 to 31 months, and stimulation experiments were performed in awake behaving animals. The novel implantable pulse generator (placed in a retroscapular location) was capable of both stimulating and performing LFP recordings concurrently. This system additionally was capable of triggering stimulation on the basis of band power changes selected by the investigator. Evoked potentials recorded with this system were obtained during anterior thalamic stimulation, with delays on the order of 50 to 100 milliseconds. Additionally, broadband suppression in hippocampal LFP activity was observed specifically with increases in the frequency of thalamic stimulation starting in the range of 40 Hz (1.0 V, 120-microsecond pulse width). With the use of a cycled thalamic stimulation pulsing regimen, the suppressed hippocampal theta band activity was shown to return between periods of stimulation.

Like thalamic stimulation, direct hippocampal stimulation was capable of broadband hippocampal LFP suppression at frequencies in the 20-Hz range and above. However, in contrast to thalamic stimulation, when direct hippocampal stimulation was performed, the most sensitive parameter for inducing decreases in theta band power was the voltage amplitude of the stimulation. Direct hippocampal stimulation at amplitudes ranging from 0.4 to 0.8 V produced increasing suppression of hippocampal LFP activity. At a stimulation amplitude of 1.0 V, an excitatory burst of activity called an afterdischarge was produced, followed by a prolonged...
Combined Direct and Indirect Revascularization Is Associated With Low Rates of Recurrent Ischemic and Hemorrhagic Stroke in Adult Moyamoya Disease

Suzuki and Takaku first coined the term moyamoya disease during the late 1960s when studying a peculiar vasculopathic disease of the brain. This rare idiopathic syndrome is characterized by luminal stenosis or occlusion of the intracranial vessels that supply the brain. 

During periods when the hippocampal LFP activity was suppressed, which was also sustained over a period of time. In summary, Stypulkowski et al have now demonstrated that the clinical benefit of localized hippocampal stimulation can be used to minimize afterdischarges. Two novel closed-loop control paradigms were demonstrated, one of which modulates the amplitude of the continuous thalamic stimulation, and the other uses a specified threshold to control the delivery of short 10-second bursts of direct hippocampal stimulation (0.9 V, 300 microseconds, 50 Hz) that successfully produced LFP suppression and maintained this suppression over extended periods of time (Figure).

The second closed-loop system demonstrated instead used continuous thalamic stimulation at a frequency of 40 Hz. Changes in recorded hippocampal theta band activity were used to modulate the amplitude of the continuous thalamic stimulation, and by this means, hippocampal activity was suppressed, which was also sustained over a period of time. In summary, Stypulkowski et al have now demonstrated (in awake behaving animals) that both local and remote deep brain stimulation can produce specific effects on hippocampal excitability. Two novel closed-loop control paradigms were demonstrated in which each successfully depressed hippocampal activity within a desired range. This kind of closed-loop deep brain stimulation paradigm is currently actively undergoing investigation with the hope that it can be applied to many different disease states, and because neuro-modulation is delivered only when necessary, it is thought that this can be used to minimize possible side effects of stimulation and to increase battery lifetime while also maximizing therapeutic benefit.

Jennifer J. Cheng, MD
William S. Anderson, MD, PhD
Johns Hopkins University School of Medicine
Baltimore, Maryland

REFERENCE

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