Translational Neuroscience

From the bench to the bedside: Brain–machine interfaces in spinal cord injury, the blood–brain barrier, and neurodegeneration, using the hippocampus to improve cognition, metabolism, and epilepsy, and understanding axonal death

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TOPICS

1. Improving cognitive impairment by decreasing hippocampal hyperactivity.
2. New brain–machine interfaces for restoring neurologic function.
3. Reversing blood–brain barrier function in Alzheimer’s and other diseases.
4. Preserving distal axon function after transection.

WHY KETOGENIC DIET WORKS IN EPILEPSY: MODULATING THE HIPPOCAMPUS TO IMPROVE COGNITIVE IMPAIRMENT[1]

Memory loss and dementia states are devastating illnesses, the prevalence of which only threatens to increase as the world’s population grows older. Most studies regarding Alzheimer’s-type dementia and the accompanying prodromal cognitive impairments have illustrated the centrality of the hippocampus in the process of memory formation, with patients with Alzheimer’s disease showing a marked reduction in hippocampal activity. On the other hand, it has recently been observed that in the prodromal states of amnestic mild cognitive impairment (aMCI), a condition where a person displays memory loss greater than would be expected for their age, there may actually be a paradoxical increase in hippocampal activity. However, the significance of the increased activity is controversial, with some theorizing that it may represent a compensatory mechanism for an otherwise failing hippocampus, and others positing that the excess activation may itself be a factor driving memory impairment.

Based on data from animal studies supporting the later hypothesis, the authors of the present study performed a clinical trial studying the cognitive effects of pharmacologically reducing this elevated hippocampal activity seen in patients with aMCI, to near-normal levels with the Food and Drug Administration (FDA)-approved agent, levetiracetam. Control and aMCI patients were studied in two treatment phases, with a washout period of 4 weeks in between. Controls received placebo medication for both phases, whereas aMCI patients received levetiracetam 125 mg BID during one phase and placebo during the other. The patients underwent functional magnetic resonance imaging with a behavioral paradigm of a 3-alternative forced choice task where subjects were presented with a series of images. A correct score was given if the subject correctly identified an image as “new” if they had never seen it before, “old” if they had seen the same image previously, or “similar” if...
the image resembled a previous item, with some detail changed. In their manuscript, the authors give as an example of such similar images 2 jack-o-lanterns with slightly different carvings. This task was chosen due to the fact the discernment of “similar” versus “old” images should rely heavily on the activity of the dentate gyrus of the hippocampus.

Using the control patients as a baseline, the authors presented the findings that pharmacologic treatment with levetiracetam diminished the elevated hippocampal activity to a level near baseline and reduced errors in which images were incorrectly judged as old and increased the number of correct responses that images were similar. Other cognitive and neuropsychological tests were not affected by the treatment and the effect of the treatment reversed within 4 weeks after discontinuation.

As a whole, this study demonstrates evidence that increased hippocampal activity in patients with mild cognitive impairment is not likely a beneficial compensatory mechanism. On the contrary, the authors demonstrate that regulation of this hyperactivity appeared to be cognitively beneficial to patients, and perhaps as importantly, easily achieved with a readily available medication.

NEW BRAIN–MACHINE INTERFACES FOR PATIENTS WITH SPINAL CORD INJURY[3-5]

In the quest to develop a neural prosthesis to help spinal cord-injured patients regain meaningful function, 2 significant incremental steps were presented in the May issue of the journal Nature. The first reports a significant advance in the development of neuroprostheses that rely on functional electrical stimulation (FES).[2] FES is a technique that uses electrical currents to activate nerves innervating extremities affected by paralysis resulting from spinal cord injury (SCI), head injury, stroke, or other neurologic disorders. Previous devices using this methodology relied on using residual proximal limb movements to trigger pre-programmed distal muscle contraction, resulting in only a few coordinated movements. Herein, Eithier et al. present an FES system that uses microelectrodes permanently implanted into the M1 hand region of the brain to record and decode the subject’s intended activity and then use these predictions to stimulate otherwise paralyzed muscle groups with the same intensity and in real time. These devices were implanted into the brains of 2 monkeys who were then subjected to local nerve blocks of the median and ulnar nerves to model an SCI patient with a C5 or C6 level. The monkeys were tasked with grasping a rubber ball, picking it up and placing it into a collection tube and were able to do so with approximately 80% success rate. In an additional test, one monkey was able to successfully exert a specified target force for 0.5 s duration while squeezing a pneumatic tube. This neuroprosthesis would provide a much finer level of control of target muscle groups than current devices, and does not rely only on intact cortical function, as opposed to distal muscle groups.

In another study, Hochberg et al. present a different form of neuroprosthesis in using a neural interface system to control a robotic arm.[3] In 2 human patients who had suffered brainstem strokes, this group used similar, implanted microelectrode arrays to record signals from M1 motor cortex neurons. The output was decoded and used to drive a freestanding robotic arm to reach for and grasp foam ball targets mounted on support stands, which would fall if incorrectly handled. In this study, participants were able to successfully maneuver the robotic arms in 3 dimensions and grab the targets with substantial precision and short timing, both of which improved over the several weeks duration of the study. Additionally, the authors report that one subject was able to use the robotic arm to grasp a cup of coffee and drink from it through a straw. Not surprisingly the video of this feat was reported widely on news outlets nationwide. Another remarkable aspect of this subject’s story was that her electrode array had been implanted some 5 years earlier and was still clearly functional.

Together, these 2 studies are cause for much hope for those suffering from spinal cord and paralyzing brain injuries to one day regain independent function.

APOLIPOPROTEINS AND THE BLOOD–BRAIN BARRIER[2]

Apolipoprotein E isoform is a major genetic risk factor for Alzheimer’s disease and is associated with Down’s syndrome dementia and poor neurologic outcome after traumatic brain injury and hemorrhage. In the present study, Bell et al. describe a possible mechanism to explain how APOE4 may increase susceptibility to brain injury and neuronal degeneration by damaging the blood–brain barrier (BBB).[4] The authors made use of transgenic mice that either lacked the murine form of APOE, or expressed one of the human isoforms, APOE2, APOE3, or APOE4. They first demonstrated that mice either lacking the murine APOE or expressing APOE4 had increased BBB breakdown as well as levels of the pro-inflammatory cytokine CypA, whereas mice with APOE2 and APOE3 did not. Pharmacologic inhibition of CypA with cyclosporine A or with knockout of the gene encoding CypA, Ppia, reversed the BBB breakdown and extravasation of deleterious proteins. They further explore the mechanism of how CypA leads to BBB breakdown, the authors examined levels of matrix metalloproteinases (MMPs) and found increases particularly of MMP9, which is known to degrade capillary basement membrane as well as tight-junction proteins. Inhibition of MMP9 by either SB-3CT a small molecule inhibitor or by siRNA reversed the leaky BBB phenotype as well as the breakdown...
of target substrates in the basement membrane and tight junctions. Similarly, the inhibition of NF-kB, a transcriptional activator of MMP9 also reduced damage to the BBB. They then show that blockade of signaling of APOE3 through a low-density lipoprotein receptor–related protein are required to downregulate CypA. However, they also revealed that APOE4 is not able to signal in this manner. In all, the authors thoroughly elucidate a mechanism by which APOE4 causes the neurovascular defects, which exacerbate neuronal dysfunction as well as provide rationale for targeting CypA for the treatment of APOE4-related disorders, such as Alzheimer’s disease.

NEW DEVELOPMENTS IN THE AXONAL DEATH PATHWAY[6]

After axotomy, the part of the axon severed from the cell body degenerates distal to the injury in a process known as Wallerian degeneration. While such clear-cut axonal transactions are rare in the clinical arena, Wallerian-like degeneration proceeds after traumatic brain and spinal cord injuries and is implicated in diseases, such as Parkinson’s, glaucoma, and multiple sclerosis. Traditionally, it has been held that the process resulted in axons that were essentially starved of nutrients from the cell body. However, as Osterloh et al. have recently reported in Science, there is mounting evidence that Wallerian degeneration is actually an active process much more akin to apoptosis, or programmed cell death, that occurs throughout the body.15 Building on earlier work, which suggested gain-of-function mutations could suppress Wallerian degeneration in the slow Wallerian degeneration mouse model, the group performed a forward genetic screen and identified a gene, dSarm in Drosophila which, when mutated, allowed for long-term survival of severed axons. Studying the mouse ortholog dSarm, Sarm1, they were able to demonstrate that cultured axons from Sarm1−/− mice were able to persist up to 72 h after axotomy, whereas wild-type axons would degenerate within 8 h. Similarly, axons appeared protected from degeneration in a sciatic nerve lesion model, lasting up to 14 days compared with 3 days for wild type. The open-probability (ie, the activity) of the ATP-sensitive K+ channels was increased in the mice with diminished BAD activity. When both BAD and the ATP-sensitive K+ channels were knocked out, the seizure-resistant phenotype was lost, indicating that reduction in seizures seen in the ketogenic diet. Like individuals on a ketogenic diet, these mice were also shown to have decreased seizure frequency and severity. To examine a possible connection between this altered metabolism and the decreases seen in seizure activity, they then examined the effects of the eliminated BAD-dependent glucose utilization on the activity on ATP-sensitive K+ channels and found that there were significant differences in the conductance through these channels. The open-probability (ie, the activity of the K+ channels was increased in the mice with diminished BAD activity. When both BAD and the ATP-sensitive K+ channel were knocked out, the seizure-resistant phenotype was lost, indicating that reduction in seizures seen in the BAD null mice was mediated through the K+ channel. These findings offer BAD as an explanation of the seizure-reducing effects of the ketogenic diet and provide a new therapeutic target for the treatment of epilepsy.

UNDERSTANDING METABOLISM AND EPILEPSY[4]

Dietary alteration as a treatment for epilepsy has been used since the time of the ancient Greeks. Presently, the ketogenic diet has regained popularity for its use in reducing seizures mainly in children with medication refractory epilepsy. However, not much is known about the mechanism by which such metabolic alterations may lead to changes in seizure frequency or severity. This month in Neuron, Gimenez-Cassina et al. lend some insight into how this may occur.6 Their study focused on the protein BAD, also known as BCL-2-associated agonist of cell death, which has been most often studied for its association with the apoptosis pathway. Previous work by the group identified a separate function of BAD as an element required for normal glucose utilization in mitochondria. Building on this, they studied the effects of altered glucose metabolism in mice lacking BAD (Bad−/− mice) or mice with mutated, nonfunctional BAD. They found that neurons and astrocytes from these mice did not utilize glucose as readily both at baseline and in situations of increased metabolic demand, and that the cells appeared to shift to the consumption of ketones. They state that this altered metabolism was analogous to what occurs in the brains of individuals on a ketogenic diet. Like individuals on a ketogenic diet, these mice were also shown to have decreased seizure frequency and severity. To examine a possible connection between this altered metabolism and the decreases seen in seizure activity, they then examined the effects of the eliminated BAD-dependent glucose utilization on the activity on ATP-sensitive K+ channels and found that there were significant differences in the conductance through these channels. The open-probability (ie, the activity of the K+ channels was increased in the mice with diminished BAD activity. When both BAD and the ATP-sensitive K+ channel were knocked out, the seizure-resistant phenotype was lost, indicating that reduction in seizures seen in the BAD null mice was mediated through the K+ channel. These findings offer BAD as an explanation of the seizure-reducing effects of the ketogenic diet and provide a new therapeutic target for the treatment of epilepsy.

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