NEUROSCIENCE

Treating brain disorders with neuromodulation

Nanoparticles, magnetic fields, and heat-sensitive ion channels are harnessed to manipulate brain activity

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Altering the activity of specific brain structures to understand their function, but also to manage their dysfunction, has been a timeless mission for neuroscientists. Classical tools for studying brain structure and function are lesioning, electrical stimulation, and chemical modulation. Although effective at the level of the brain structure, these tools lack a high degree of selectivity and specificity. More advanced neuromodulation techniques are overcoming these limits, including optogenetic approaches and chemogenetic tools [such as designer receptors exclusively activated by designer drugs (DREADD)]. On page 1477 of this issue, Chen et al. (1) add magnetothermal neuromodulation to this list. The approach allows specific neurons to be activated by heat-emitting nanoparticles that respond to externally applied magnetic fields.

Chen et al. introduced the heat-sensitive calcium ion channel TRPV1 into neurons (via viral delivery of the encoding gene) located in the ventral tegmental area of the mouse brain. Four weeks later, magnetic nanoparticles were injected into the same region, where they were detected in the extracellular space (whether they are internalized by any cell in vivo remains to be shown). Mice were then exposed to an external alternating magnetic field that allows specific neurons to be activated by heat-emitting nanoparticles that respond to externally applied magnetic fields.

The development of new tools for intracranial neuromodulation (see the figure) evokes a concept hypothesized by Nobel Laureate António Egas Moniz in the first half of the 20th century—that a dysfunctional circuit of Papez (medial limbic circuit that connects the hypothalamus to the cortex) underlies major affective disorders. He and others intervened surgically with lesions of the frontal cortex by a transorbital route (lobotomy). The idea was to destroy connective nerve fibers or specific brain tissue, but the procedure only improved symptoms in some patients temporarily, and the risks included serious affective and cognitive side-effects such as apathy.

In the second half of the 20th century, electrodes placed temporarily in deeply situated areas of the brain became more popular. Limbic regions were thus stimulated to modulate affective behaviors of patients (3). A well-known animal study demonstrated that an attacking bull could be stopped instantly when an electrode, placed in its caudate area, was activated by a remote controller (4). Although these methods were hypothesis-driven, their main weakness was the lack of a robust scientific base, and they
Key neuromodulation approaches

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Trends in treatment. Techniques to alter neuron activity in the brain shifted from a macrocircuity focus to one that now concentrates on modulating specific populations of neurons. The time periods indicate the global course of development.

fell into disuse with the rise of drugs targeting the central nervous system.

An increased understanding of the neuronal function was the determining factor for the successful application of deep brain stimulation of the subthalamic nucleus in patients with Parkinson’s disease. In contrast to earlier techniques of electrical stimulation in which electrodes are placed temporarily in the brain and stimulated by external devices to simply drive neuronal activity, deep brain stimulation involves the chronic implantation of electrodes driven by an internal pacemaker to counteract abnormal neuronal activity. Studies on basal ganglia function in animal models of Parkinson’s disease (5, 6) paved the way for clinical application of deep brain stimulation of the subthalamic nucleus in 1993 (7). Since then, the technique has been applied in other neurological and psychiatric disorders, both in translational models and patients (8). In some patients, clear therapeutic effects have been seen, such as in dystonia, Tourette’s syndrome, and obsessive-compulsive disorder. However, for other mental conditions such as intractable depressions (resistant to drugs, behavioral and electroconvulsive treatments) the approach has failed (9). Interestingly, the same methodology of deep brain stimulation for treating Parkinson’s disease has been prescribed for patients with other neurological and psychiatric disorders, mainly because of limited progress in drug discovery for those disorders and the availability and safety of technology for deep brain stimulation. The risk here is that deep brain stimulation for these conditions, while hypothesis driven, lack a robust scientific base. Its application without understanding the fundamental neuronal underpinnings of the disorders could lead to negative outcomes, which could influence research in the field, as well as the interest of society.

Moreover, even with relevant knowledge, minimal invasiveness, safety, and disorder and symptom specificity, clinical success is not guaranteed. For example, clinical studies with intracranial adeno virus-based delivery of glutamic acid decarboxylase (10) or glia cell line–derived neurotrophic factor (11) had unfavorable outcomes despite promising results in translational models.

After a long period of technological downtime for treating brain disorders (12), a number of new approaches have been introduced. The DREADD approach, in which receptors are engineered to respond to synthetic small-molecule ligands, is gaining momentum as a neuromodulatory approach. For example, in an animal model of epilepsy, this approach attenuated focal neocortical seizures (13). In the field of deep brain stimulation, promising methods include adaptive/closed-loop deep brain stimulation (14) and current steering (15). In the former, stimulation is only activated when pathological neuronal activity starts. The latter approach involves the control of the direction of stimulation to avoid current spread to neighboring regions. For ischemic surgery, ultrasound-based approaches are receiving interest. Speeding up these developments seems to be linked to the failure of systemic drug–based approaches to deliver breakthrough therapies for neurodegenerative and psychiatric diseases.

It is unclear whether or not hypothesis-driven molecular approaches that require viral delivery tools and genetic manipulations will enter the clinical arena. Meanwhile, technologies such as remote magnetothermal neuromodulation developed by Chen et al. could be used widely in translational models to enhance our knowledge of the brain’s microcircuitry in normal and disease states. As with the development of deep brain stimulation for patients with Parkinson’s disease, this new knowledge could spur the progress of future therapies—neuromodulation-based or not—for patients with brain disorders.

REFERENCES

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