factors are expressed. Consequently, global analysis of myelination could fail to detect important changes resulting from loss of a growth factor secreted by only a subset of unidentified axons. Systematic analysis of transgenically marked neuron subtypes in zebrafish should help overcome this limitation.

Koudelka *et al.* raise a final important point in their discussion. Although the field has been firmly focused on how myelin plasticity could modulate the timing and frequency of electrical impulses to contribute to learning, this possibility remains largely hypothetical. An alternative possibility is that vesicle secretion from rapidly firing axons attracts myelin to provide metabolic support for the axon. Distinguishing between these possibilities will require coordinated investigation of the electrophysiological, functional and metabolic properties of individual classes of myelinated axons.

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Neuroendocrinology: Electromagnetogenetic Control over Feeding and Glucose Metabolism

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Cutting-edge experiments show a new means to control the activity of specifically genetically targeted neurons in the hypothalamus using electromagnetic force. At the flip of a switch, the system bidirectionally regulates feeding behavior and glucose homeostasis, demonstrating wireless control over deep brain regions and their strong influence over energy balance.

The ability of magnetic mind control is no longer limited to fictional characters in superhero films or comic books. As they report in a recent study in *Nature*, Stanley *et al.* [1] have genetically encoded ferrous material inside neurons of mice, offering wireless, non-invasive, cell-specific control over neuronal

activity deep inside the brain through radio waves or magnetic strength. To demonstrate the applicability, the paper describes an innovation that successfully controls glucose-sensing neurons in the ventromedial nucleus of the hypothalamus (VMH) to bidirectionally regulate feeding behavior and glucose metabolism, representing a powerful methodological bedrock for future exciting discoveries in neuroscience.

Tight control over cellular activity is a long-sought goal of systems neuroscience, inspiring the development of several technologies. The conventional knockout mouse has infused all fields of medicine [2] but may come with caveats since it lacks a gene in every cell from the beginning of life. Escaping this side effect, cell-specific inducible editing is a vast improvement allowing gene expression to be specifically and temporally regulated, and even reversibly controlled [3–5].

Although these seminal techniques provide a wealth of information about biology, the urge to switch neurons on or off at desired time points has motivated the search for advanced technologies. Optogenetics has revolutionized neuroscientific research since it offers the selective control of neurons that have been tailored to express light-sensitive ion channels [6]. When exposed to beams of light, fluxes of ions through these channels lead to fast neuronal activation or inhibition. One of the advantages of optogenetics is high spatial and temporal precision. By shining light on nerve fibers originating from distinct neurons, the impact of connections between neuronal networks on glucose metabolism can be analyzed [7]. Chemogenetics, based on the expression of engineered receptors that are unresponsive to endogenous molecules but reactive to a drug [8], is another attractive approach because the drug can be easily administered to drive or curb neuronal activity and because the method can be applied to target a large number of neurons without specialized equipment. While these new technologies have provided significant advances, chemogenetics doesn't provide instant time- and location-dependent control, and optogenetics is inherently invasive and requires permanent brain implants.

An alternative that holds the potential to by-pass many of these limitations is the idea of using magnetic fields as a way to remotely control neurons [9]. Although exogenous magnetic nanoparticles have recently been shown to regulate gene and protein expression [10], one key question remained unanswered: can genetically encoded magnetic matter synthesized in the neurons be adapted to manipulate excitatory and inhibitory synaptic transmission in the brain?

Building on their own prior work [10,11], Stanley *et al.* [1] have now done just that to neurons in a hypothalamic subnucleus, the VMH. Early lesioning studies revealed that the VMH is involved in the recognition of satiety because damage to the VMH resulted in voracious eating and obesity [12]. While those experiments defined the VMH as a satiety center, recent data have assigned this nucleus a much broader role in the control of energy homeostasis [13,14], and chronically altering VMH neuron activity is now known to affect peripheral glucose metabolism [15,16]. Distinct VMH neurons work as glucose sensors and balance the release of hormones that defend against hypoglycemia when glucose drops too low [17,18]. While all neurons utilize glucose as fuel, VMH neurons quickly change their firing rate in response to changes in brain glucose levels.

According to their fundamental role in glucose monitoring, and given that precise control of the levels of glucose — the important energy substrate for neurons — is critical for the organism, VMH neurons represent an ideal candidate to evaluate the relevance of remotely controlling a biological response using a radio. The concept relies on coupling a temperature-detecting calcium channel called TRPV1 (commonly known as the receptor for the irritating compound in chilli pepper) to a form of ferritin (an iron-storing protein) that has been modified to respond to electromagnetic waves. The energy of the waves, which travel readily through tissues, is absorbed by the ferritin, heating it and causing it to undergo motion. This movement is transferred to TRPV1, by virtue of its fusion to ferritin, changing the confirmation of TRPV1 and triggering influx of calcium, leading to neuronal activation.

Stanley *et al.* [1] capitalized on the advantage of the Cre–LoxP method for tissue-specific expression and generated a genetic construct in which the ferritin–TRPV1 fusion protein can be expressed in VMH neurons expressing the enzyme Cre recombinase under a cell-specific promoter (Figure 1). For expression in the VMH, they packed replication-deficient adenoviral particles with the construct and injected them into the VMH of transgenic glucokinase–Cre mice, in which Cre is expressed in glucose-sensing neurons. Although the virus will infect many neurons, the ferritin–TRPV1 fusion will only be expressed in glucokinase-expressing neurons, representing a Cre-dependent magnetogenetic system and eliminating the use of exogenously delivered iron nanoparticles.

Proving the method's specificity, the authors confirmed that radio waves increased intracellular calcium and activated the neurons of interest. The level of calcium response and excitation was moreover found to be specific to TRPV signaling and proportional to the radio waves' signal strength and duration. As a compelling verification of the method's efficacy, exposure of living mice expressing the construct in the VMH to radio waves robustly increased peripheral blood glucose. The authors also observed that activation of VMH neurons halved circulating insulin concentrations, while increasing plasma glucagon levels and the expression of genes involved in glucose synthesis in the liver, suggesting that activating the glucoresponsive neurons regulated the abundance of key glucoregulatory hormones from the pancreas and activated gluconeogenesis. Thus, it seems that activating this subpopulation of VMH neurons makes the brain think it's low on sugar. The scientists also compared the rise in blood glucose induced by radio waves with that achieved by stimulating VMH neurons optogenetically. Photostimulation mirrored treatment with radio waves since laser light acutely raised blood glucose concentrations. Thus, activating VMH neurons via radio waves represents a feasible approach for

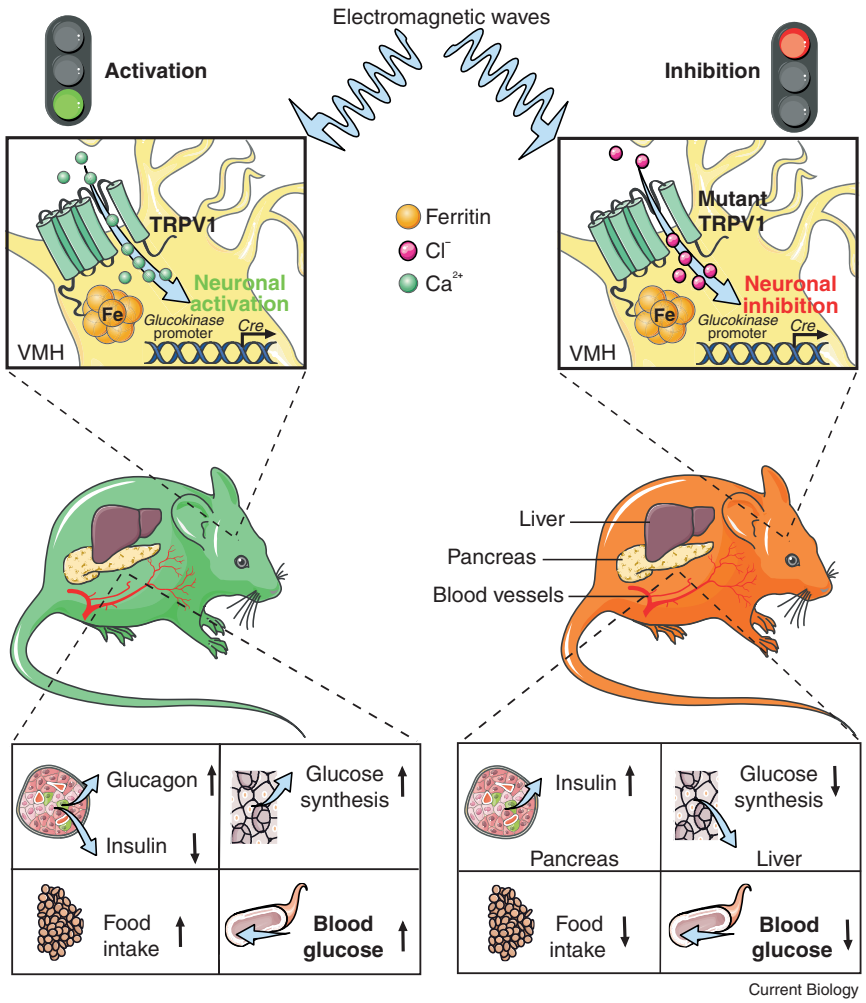

Figure 1. Electromagnetic control over neuronal function bidirectionally regulates feeding behavior and glucose metabolism.

Stanley *et al*. [1] have expressed genetic fusion constructs consisting of TRPV1 and ferritin (Fe) selectively in neurons of the ventromedial nucleus of the hypothalamus (VMH) expressing Cre recombinase under the control of the glucokinase gene promoter. To enable bidirectional control, the authors generated two different constructs: one in which Fe was coupled to TRPV1, and one in which Fe was linked to a mutated form of the channel (mutant TRPV1). Upon stimulation of mice expressing the TRPV1–Fe fusion protein in VMH neurons with electromagnetic waves, the influx of calcium ions (Ca^{2+}) through TRPV1 resulted in neuronal activation, followed by a reduction in circulating insulin, whereas glucagon, liver gluconeogenesis, feeding and blood glucose levels increased. Thus, activating VMH neurons regulated pancreatic hormones and glucose production to raise blood glucose. Conversely, an influx of chloride ions (Cl^-) and neuronal inhibition were seen when mutant-TRPV1–Fe was exposed to electromagnetic waves. *In vivo*, stimulation of VMH neurons expressing mutant-TRPV1–Fe promoted insulin release, while glucose synthesis, feeding and blood glucose levels decreased.

studying the neural control of glucose metabolism.

A novel tool in the present study is a mutated form of TRPV1 that is permeable to chloride ions. When chloride ions over a certain threshold flow into a neuron, they facilitate neuronal inhibition. Inhibiting the VMH neurons elevated plasma insulin levels whilst conversely suppressing the expression of liver gluconeogenic genes, concomitant with markedly lower blood glucose. This finding suggests that keeping blood glucose levels constant depends on the tonic activity of hypothalamic neurons and further substantiates the capability of VMH neurons to directly influence the secretion of hormones with the purpose of maintaining the glucose equilibrium. The link to counter-regulation was further substantiated by observations made in mice injected with a non-metabolizable glucose analog, a paradigm that mimics glucose shortage in the brain. Inhibiting VMH neurons blunted the hyperglycemic response, confirming that these neurons are important in combatting hypoglycemia, a condition that may threaten the organism.

To test whether a magnetic field could also modulate neural activity, given ferritin's paramagnetic properties [11], the researchers exposed neural cells expressing one of the new constructs to an electromagnet. Magnetic force indeed increased TRPV-dependent intracellular calcium levels, depolarized and increased the firing rate of the neurons expressing the excitatory construct, whereas it increased chloride ion content and quelled the activity of neurons expressing the mutated TRPV1 version. Moreover, exposure of fasted mice carrying either the excitatory or inhibitory construct to a magnetic field led to changes, although subtle, in food intake; whereas activation triggered feeding, inhibition curbed eating, assigning VMH neurons a critical role in modulating fuel availability when energy resources are low.

That this system [1] tampers with the action of genetically defined neurons in a bidirectional fashion adds versatility. The activity of any cluster of even dispersed cell types could logically be made accessible. Furthermore, it may extend beyond TRPV1, a large protein widely distributed throughout the brain. Tethering ferritin to another substrate converting the electromagnetic radiation to other intracellular signals, or tuning ion selectivity, may open doors to the study of a range of neuronal populations and processes. The fact that the amount of calcium influx varied with the energy supplied suggests that the physiological response can be modulated, which could allow for the control of cells differentially regulated at different ion concentrations, while optimized to respond to magnetic fields only and not to the endogenous ligands. An additional interesting observation is how rapidly radio wave treatment activated the fusion protein and took over the control of systemic glucose levels, offering fast interrogation of neural activity, similar to

optogenetic-based approaches, and highlighting the vital role of VMH neurons in glucose homeostasis.

The paper by Stanley *et al.* [1] and recent articles on the same timely subject [19,20] are important. Electromagnetogenetics requires multiple and unique components, however, and time will tell if it will be applied outside the original laboratories. We hope that this state-of-the-art method will become a broadly applicable tool for neuroscientists, used by more than the exclusive number of comic book superheroes born with the power to control metal.

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Cell Biology: ERADicating Survival with BOK

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Mechanistic insights into the function of the pro-apoptotic BCL-2 family member BOK have remained elusive. A recent study shows that healthy cells constitutively degrade BOK via the ER-associated degradation and ubiquitin–proteasome pathways; following proteasome inhibition, BOK is stabilized to initiate a unique pro-apoptotic death program.

The typical day for the average adult includes eliminating billions of stressed or superfluous cells from a broad range of tissues to sustain homeostasis and prevent disease. Frequently, these targeted cells utilize a death program termed apoptosis, which is characterized by the orchestrated dismantling of critical cytoplasmic and nuclear components and the rapid detection and removal of cellular corpses by phagocytes [1]. As with many aspects of cell biology, when apoptotic signaling goes awry, disease ensues: too much apoptosis can promote neurodegeneration; too little can promote tumorigenesis and resistance to chemotherapeutic agents. Cellular survival and commitment to apoptosis is ultimately mediated by the B-cell lymphoma 2 (BCL-2) family of proteins, which is composed of approximately 20 members [2]. The anti-apoptotic BCL-2