EDITORIALS

Arthroscopic Surgery for Osteoarthritis of the Knee?

Robert G. Marx, M.D.

Orthopedic surgeons perform arthroscopic surgery in many joints of the extremities, most commonly the knee. Two or three incisions are routinely made, each measuring approximately 7 mm. The knee is inflated with fluid under pressure, with the assistance of a pump, to facilitate visualization. Because of advances in fiberoptics and instrumentation, many knee procedures (e.g., ligament reconstruction, meniscus excision and repair, synovectomy, and removal of loose bodies) can now be performed arthroscopically, with greater ease and accuracy and fewer complications than with an open incision. However, as with any surgical procedure, arthroscopic surgery is not appropriate for all patients with knee conditions, just as open-heart surgery is not indicated for all patients with cardiac disease.

In this issue of the *Journal*, Kirkley et al. report the results of a well-performed randomized trial of the effects of arthroscopic surgery as compared with nonoperative treatment for patients with osteoarthritis of the knee.[1] In a previous randomized trial, Moseley and colleagues had demonstrated that arthroscopic débridement for advanced arthritis was no better than sham surgery in a predominantly male population of U.S. veterans.[2] Kirkley and colleagues studied a civilian population, including a more representative sample of men and women, and used a well-validated primary end point, the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, which assesses pain, stiffness, and physical function. Kirkley et al. concluded that arthroscopic surgery was not more effective than nonoperative treatment, which included physical therapy (one session per week for 12 weeks followed by an unsupervised program at home), patient education, and the stepwise use of acetaminophen, nonsteroidal antiinflammatory drugs, glucosamine, and the injection of hyaluronic acid. These results provide strong support for the conclusion of Moseley et al. that arthroscopic surgery is not effective therapy for advanced osteoarthritis of the knee.

An important caveat is that the lack of efficacy of arthroscopic surgery in this trial does not imply that it has no role in the treatment of patients who may have osteoarthritis and also another knee condition, such as a symptomatic meniscal tear. Kirkley et al. explicitly excluded from the trial patients who had “large meniscal tears, as detected by clinical examination or, in a minority of cases, by magnetic resonance imaging [MRI],” in whom surgery was considered appropriate. These exclusions made it less likely that the study would find a benefit to arthroscopic surgery as compared with nonoperative care. The results, however, are applicable to the large number of patients with osteoarthritis of the knee, without another apparent condition warranting arthroscopic intervention, who present for pain management.

The selection of patients who are likely to benefit from surgery is critical yet can be challenging. In contrast to other surgical disciplines (e.g., cancer surgery) in which outcomes are closely correlated with specific anatomical lesions and indications for surgery are well delineated, decision making in elective orthopedic surgery is based on symptoms and disabilities that constitute an assessment of quality of life, which is much more difficult to quantify. Anatomical and MRI abnormalities in orthopedic surgery are not consistently correlated with symptoms,[3] and correction of abnormalities does not necessarily translate into functional improvement.

A particularly relevant example is a case in which meniscal findings coexist with arthritis of the knee.[4] In this issue of the *Journal*, Englund et al. report a high prevalence of meniscal symptoms on MRI of the knee in middle-aged and elderly patients, particularly among those with osteoarthritis,[5] underscoring the frequency with which these conditions coexist. Many of the patients with meniscal tears visualized on MRI reported no knee symptoms, emphasizing that identifying a tear in a person with knee pain does not mean that the tear is the cause of the pain. Furthermore, among patients with both osteoarthritis and a meniscal tear who have pain, it can be difficult to determine which of the two is the major cause.

To illustrate the subtleties involved in clinical decision making for these patients, I present two hypothetical examples. These patients are at opposite ends of the spectrum with respect to prognosis after arthroscopic surgery, and both would have been eligible for the study by Kirkley et al. Patient 1 is a 48-year-old woman with a 5-month history of medial knee pain after an injury involving twisting. Radiographs indicate no narrowing of the joint space and a small medial tibial osteophyte, and MRI reveals a clear, medial meniscal tear. She has knee pain with daily activities, particularly twisting, squatting, and running. Patient 2 is a 67-year-old woman with gradually worsening pain over a period of 4 years and difficulty walking because of pain. Radiographs show medial-compartment bone-on-bone osteoarthritis with three degrees of varus malalignment. MRI shows a meniscal tear.

Arthroscopic surgery confers a good prognosis for Patient 1 because she is younger and has mild osteoarthritis, and her history of injury and the nature of symptoms suggest that the meniscal tear is the cause of the pain. Her symptoms would be unlikely to resolve without surgery. In contrast, the symptoms of Patient 2 are most likely attributable to osteoarthritis, and arthroscopic surgery is unlikely to provide benefit.[6]

These hypothetical examples are oversimplifications, since there are many other variables that affect prognosis. However, they illustrate the need to individualize decision making with respect to arthroscopic surgery for patients with osteoarthritis of the knee.

In summary, the study by Kirkley et al., combined with other evidence, indicates that osteoarthritis of the knee (in the absence of a history and physical examination suggesting meniscal or other findings) is not an indication for arthroscopic surgery and indeed has been associated with inferior outcomes after arthroscopic knee surgery.[7] However, osteoarthritis is not a contraindication to arthroscopic surgery, and arthroscopic surgery remains appropriate in patients with arthritis in specific situations in which osteoarthritis is not believed to be the primary cause of pain.[8] Surgeons must practice evidence-based care and use sound clinical judgment to make the best decisions for individual patients.

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Renal Phosphate–Transporter Regulatory Proteins and Nephrolithiasis

Moshe Levi, M.D., and Sophia Bruesegem, Ph.D.

Nephrolithiasis is a common disorder, and idiopathic hypercalciuria is the most frequent metabolic disorder associated with nephrolithiasis.[1] Several studies have shown that subjects with idiopathic hypercalciuria have phosphaturia or renal phosphate leak. In fact, a study that measured the tubular maximal reabsorption of phosphate (TmP, or maximal renal phosphate threshold) normalized for the glomerular filtration rate (GFR) (the TmP:GFR ratio) in 207 subjects with calcium nephrolithiasis reported that 20% of persons with normal parathyroid function in whom stones formed have a decreased TmP:GFR ratio.[2] The associated mild hypophosphatemia results in increased 1,25-dihydroxyvitamin D production, which causes increased intestinal phosphate and calcium absorption. The combination of hypercalciuria from the increased intestinal calcium absorption and the hyperphosphaturia favors the formation of calcium phosphate complexes that can result in nephrolithiasis (Fig. 1A).

The cause of phosphaturia in subjects with nephrolithiasis has been the subject of several recent investigations, and attention has centered on the potential role of the renal phosphate transporters. Regardless of the serum phosphate concentration, phosphate is freely filtered across the glomerulus and reabsorbed along the renal tubule, mostly the proximal tubule, through two distinct sodium phosphate transporters that are dependent on the sodium gradient: NPT2a (encoded by the *SLC34A1* gene) and NPT2c (encoded by the *SLC34A3* gene).

Studies of Npt2a-knockout mice indicate that NPT2a mediates the reabsorption of 70% of the filtered phosphate. Recently, a missense mutation in Npt2a in mice has been shown to impair renal phosphate transport and result in nephrolithiasis, a result similar to that seen in the NPT2a-knockout mouse.[3] Similarly, a report in the *Journal* concerning subjects with nephrolithiasis and osteoporosis associated with hypophosphatemia who had an impaired TmP:GFR ratio identified heterozygous mutations in the NPT2a gene.[4] Furthermore, follow-up studies indicated that although genetic variants of NPT2a are not rare, they do not seem to be associated with clinically important renal phosphate leak.[5]

Recent studies, however, have definitively identified mutations of NPT2c as the cause of hereditary hypophosphatemic rickets with hypercalciuria, which is an autosomal recessive inherited disorder of mineral and bone metabolism. It is characterized by hypophosphatemia, rickets, and an increased serum 1,25-dihydroxyvitamin D concentration resulting in secondary absorptive hypercalciuria; it is also associated with renal calcification and nephrolithiasis. Another recent study identified new NPT2c mutations that lead to mistargeting of NPT2c protein and uncoupling of sodium phosphate cotransport as the cause of hereditary hypophosphatemic rickets with hypercalciuria.[6]

The study reported by Karim et al. in this issue of the *Journal* identifies yet another potential new and interesting mechanism of phosphaturia: mutations in the sodium–hydrogen exchanger regulatory factor 1 (NHERF1, also known as EBP50).[7] NHERF1 is a PDZ protein that interacts with the C-terminal tail of NPT2a[8] and also NPT2c[9] and plays an important role in the trafficking and transcriptional regulation of NPT2a[10] (Fig. 1B).

In the study by Karim et al., the authors identified three NHERF1 mutations in seven patients who had lower TmP:GFR ratios, lower serum phosphate concentrations, and higher serum 1,25-dihydroxyvitamin D concentrations than controls. Despite their normal PTH concentrations, the patients had increased urinary cyclic AMP (cAMP) concentrations. The authors then conducted experiments in which wild-type or mutant *NHERF1* complementary DNA (cDNA) was expressed in opossum kidney cells, a model of proximal tubule cells that express NPT2a and the PTH type 1 receptor (PTH1R). Although there were no significant differences in the baseline cAMP concentrations or phosphate uptake between the transfected cells and wild-type cells, a challenge with PTH resulted in greater cAMP stimulation and greater inhibition of phosphate transport in the cells expressing the mutant NHERF1 than in the wild-type cells. Since in addition to its activation of the

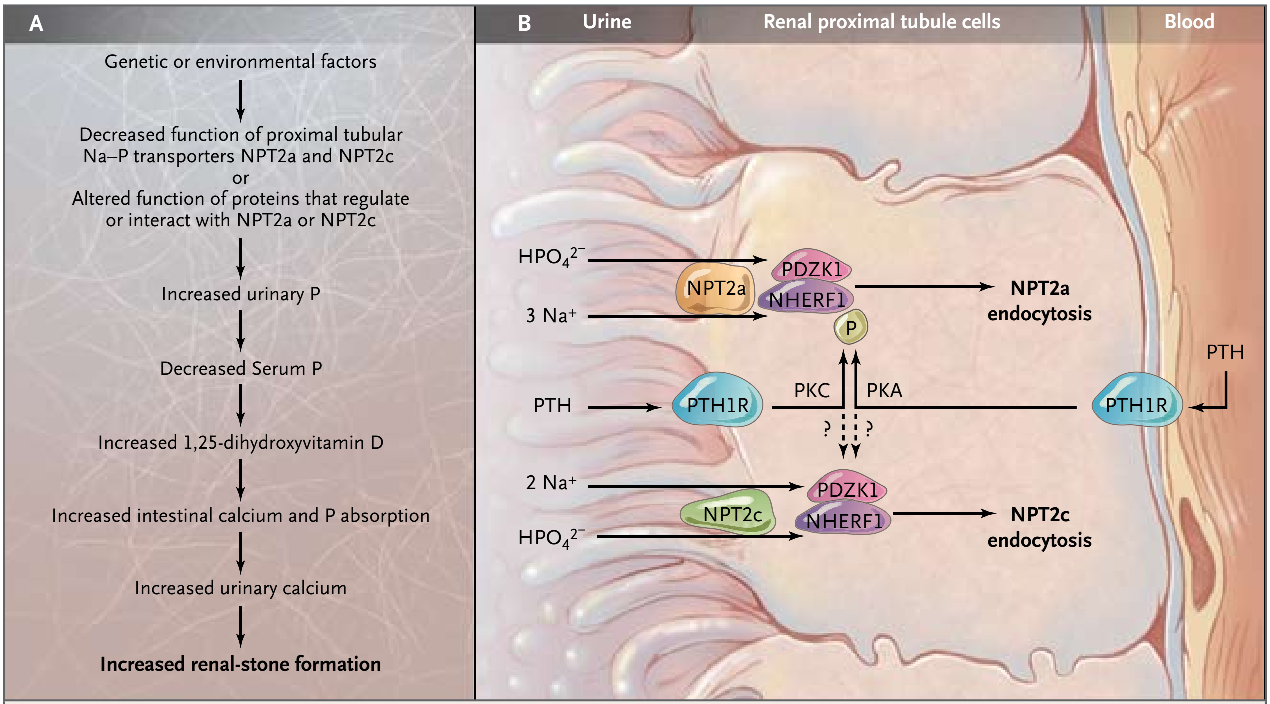

Figure 1. Postulated Mechanisms of Nephrolithiasis and Phosphate-Transport Inhibition.

Panel A shows postulated mechanisms of how a primary renal phosphate leak could result in hypercalciuria and formation of renal stones. Panel B shows postulated mechanisms of how parathyroid hormone (PTH) signaling through the PTH type 1 receptor (PTH1R) in the apical brush-border membrane and basolateral membrane results in the phosphorylation of NHERF1, which leads to disassociation of NHERF1–NPT2a complexes and endocytosis (internalization) of apical NPT2a protein and inhibition of phosphate transport. The mechanisms of interactions between PTH and PDZ domain containing 1 protein (PDZK1) and of PTH-induced NPT2c endocytosis remain unknown. PKA denotes protein kinase A, and PKC protein kinase C.

cAMP–protein kinase A signaling pathway, PTH activates the phospholipase C signaling pathway, the authors then measured cellular calcium and inositol phosphate concentrations and found no alterations in response to PTH.

NHERF1 deficiency in mice and NHERF1 inhibition in cells have been definitively shown to impair the transport activity and expression of NPT2a in the apical membrane, and NHERF1 phosphorylation by PTH has been shown to be important in the internalization of NPT2a.[11] However, it is not clear how the currently described NHERF1 mutations mediate abnormalities of phosphate transport in humans, since expression of the mutant *NHERF1* cDNA per se had no effect on phosphate transport. More in vivo studies will be needed to clarify this issue. In addition, it will be important to determine whether these mutations directly modulate the transport activity and expression of NPT2c as well as NPT2a and whether there are secondary effects on sodium–potassium–ATPase, which is also regulated by PTH through an NHERF1-dependent pathway and may regulate sodium phosphate cotransport by means of decreased generation of the sodium gradient.

Recent studies also indicate that NHERF1 interacts with mouse urate transporter 1 to regulate uric acid transport in the renal proximal tubule and that NHERF1-knockout mice have increased uric acid excretion.[12] Even more recent data also indicate a potential interaction between NHERF1 and the renal-proximal-tubule sodium sulfate transporter NaSi-1, but it is not known whether NHERF1-knockout mice have increased urinary sulfate excretion.[13] Obviously, it is important to know whether the subjects with NHERF1 mutations also had abnormalities in uric acid or sulfate excretion, since these are also highly relevant to nephrolithiasis.

Other mutations may be relevant to sodium phosphate transport and nephrolithiasis. Potential mutations of another PDZ protein, PDZ domain containing 1 protein (PDZK1; also called CAP70, PDZD1, and NHERF3) should be considered, since a recent study demonstrated that NPT2c interacts with PDZK1.[9] In addition, mutations in chloride channel 5 (CLCN5), a member of the CLCN5 family of voltage-gated chloride channels and transporters and the cause of Dent's disease, can also cause phosphaturia. Clcn5-knockout mice have a defect of proximal tubular endocytosis that results in an increased luminal PTH concentration and stimulation of the apical PTH1R, causing increased endocytosis of NPT2a and activation of 1α,25-hydroxyvitamin D hydroxylase, which may result in increased 1,25-dihydroxyvitamin D concentrations.[14] Furthermore, alterations in fibroblast growth factor 23 (FGF-23) and klotho also regulate the sodium phosphate transporters, and gain-of-function mutations could cause hyperphosphaturia; however, the FGF-23–klotho complex is known to inhibit 1α,25-hydroxyvitamin D hydroxylase and, in the absence of an increased 1,25-dihydroxyvitamin D concentration, would not be expected to cause hypercalciuria or nephrolithiasis.[15]

Therefore, in addition to documenting the potential role of mutations of the renal sodium phosphate transporters, this study suggests that mutations in proteins interacting with sodium phosphate may also play an important role in renal phosphate leak and nephrolithiasis. This set of findings opens a new area in nephrolithiasis research for further investigations to unravel the causes of this interesting and important disorder.

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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Turning Thought into Action

Leigh R. Hochberg, M.D., Ph.D.

Patients with spinal cord injury, subcortical stroke, neuromuscular diseases (including amyotrophic lateral sclerosis), and limb amputation have at least two characteristics in common: a brain that wants to direct movement and a body that fails to respond accordingly. Despite intact cortical function, central motor commands in persons with these paralyzing disorders are "disconnected" from their targets, with the neural impulses of intended movement unacknowledged by the downstream central or peripheral nervous system. Pharmacologic, cellular (including stem-cell), and other therapies are designed to repair the injury on-site, but what if the lesion could simply be bypassed with the use of a new pathway for these signals to control either one's own limbs or assistive devices such as prosthetic limbs? A recent study by Velliste et al.[1] represents a step toward these goals.

The primary motor cortex (M1) is vital for generating the fine finger and hand dexterity of monkeys and humans. Recordings of single M1 neurons in monkeys performing manual tasks such as gripping a joystick have revealed an association between changes in the action-potential firing rate of these neurons and the dynamics[2] and kinematics of hand movement. In particular, some M1 cells demonstrate "directional tuning": they fire at greatest frequency when an animal reaches in a particular direction (the "preferred direction" for that cell) and at minimum frequency when the animal reaches in the opposite direction (Figure 1).[3] This can be modeled as a cosine tuning curve by plotting firing rate against direction of movement; knowing a cell's firing rate, one can then predict (with varying degrees of accuracy) the direction of limb movement.

Not much can be gleaned from observation of the instantaneous firing rate of a single neuron, particularly if one wishes to predict the movement of a multijointed limb in three-dimensional space. With recent advances in technology and surgical techniques, however, tiny arrays of microelectrodes can be inserted into the cortex, enabling the recording of activity from a hundred or more neurons in real time. A relatively small ensemble, or population, of directionally tuned M1 neurons allows the location of an animal's hand to be predicted, for example, while the animal moves a joystick to control a cursor in a video game. If the joystick controlling the cursor is then disconnected, that neural output can be decoded into a command signal to move a two- or three-dimensional cursor directly.[4,5] In such experiments, the animal often stops making overt movements of its hand, instead controlling the cursor by "intent" — neural power — alone.

Velliste et al. focused on the neural control of a prosthetic arm for carrying out a task of clear importance — reaching for food, grasping it, and bringing it to the mouth. Two monkeys were trained to use a joystick coupled to a prosthetic arm with shoulder and elbow joints and a terminal gripper. Over 2 to 3 months, control of the prosthetic arm was shifted gradually from joystick to neuron, with neural control driven by a "population vector": the sum of the activity of the simultaneously recorded, directionally tuned M1 neurons. Velliste et al. used cortical activity to define the continually updated end-point location; the robot software then converted this command into the appropriate joint movements. Both monkeys used the robot arm to reach repeatedly for food (such as a marshmallow), grasp it, bring it to the mouth, and release it, all driven solely by the real-time decoding of a small number of motor cortical cells. Moreover, the authors also trained one of the monkeys to open and close the robot gripper using neural activity from this same population of neurons. (For the other animal, the robot gripper opened and closed automatically, depending on the location and movement of the robot arm.)

The monkeys in the study were neurologically intact, but the results are relevant to the development of neural interfaces to help people with paralysis. Our group has previously described a

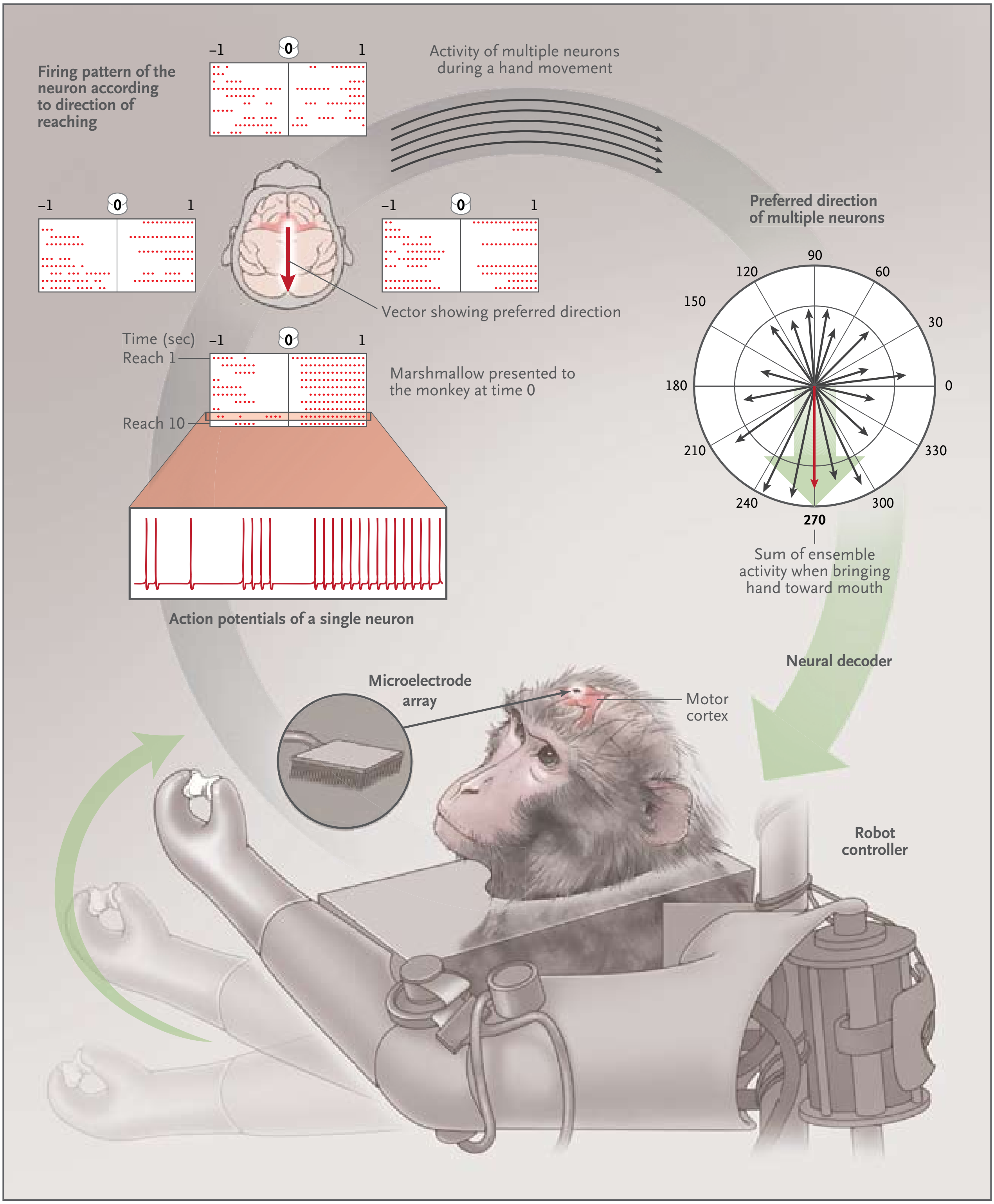
Firing pattern of the neuron according to direction of reaching
–1
0
1
Activity of multiple neurons during a hand movement
Preferred direction of multiple neurons
Vector showing preferred direction
Time (sec)
Reach 1
Reach 10
Marshmallow presented to the monkey at time 0
90
120
60
150
30
180
0
210
330
240
300
270
Sum of ensemble activity when bringing hand toward mouth
Action potentials of a single neuron
Neural decoder
Microelectrode array
Motor cortex
Robot controller

Figure 1 (facing page). Control of a Robotic Arm by Neural Activity.

Velliste et al.[1] recently reported an advance in training monkeys to use a robotic arm through impulses generated by the motor cortex. An array of microelectrodes is placed into the motor cortex, enabling the action potentials from dozens of neurons to be recorded simultaneously. If the animal reaches in a specific direction, the activity of some neurons will be directionally tuned; the particular neuron shown in this figure is more likely to fire when the animal reaches downward — in this case, after presentation of a marshmallow at time 0. The preferred direction is illustrated by the downward-pointing vector (red arrow). The firing patterns of multiple neurons, which reflect randomly distributed preferred directions, are graphed, with the length of each vector indicative of each neuron's firing rate during movement of the hand. The activity of a population of neurons is fed into a neural decoder. Decoders use a variety of computational techniques to determine the direction of intended limb movement from the neural population activity and in turn feed that command to a robot controller, which moves the robot arm in the desired direction.

man with tetraplegia from a C4 spinal cord injury who used M1 signals similar to those recorded in the two monkeys to control a computer cursor, a prosthetic hand, and on one occasion, a robot arm for grasping and transporting an object.[6] In this and other cases, the signal extracted from M1 became useful for device control in a matter of minutes. This suggests that the cortical activity associated with intended movement can persist despite paralysis and that this signal could be harnessed for natural reacquisition of one's own limb or to drive an assistive device (such as a wheelchair) or, for amputees, to control a prosthetic limb.

Challenges lie ahead, however, in creating a system that provides around-the-clock, decades-long neural control of implanted or external devices. Most implanted neural-interface systems require a percutaneous connector; fully implantable systems should reduce surgical and postoperative risks and increase the potential of using implanted electrodes in multiple brain regions to provide finer device control. Hardware used to separate and amplify neural signals needs to be miniaturized and automated. Like deep-brain stimulators for movement disorders, these systems should be usable by and beneficial for patients without a caregiver — or a laboratory neurophysiologist — needing to set up the equipment every day. Clinical trials for safety and feasibility are necessary, in part to test the efficacy of these devices in the context of different disease processes. That said, the knowledge gained through the work of Velliste et al.[1] and similar preclinical studies not only provides a better understanding of the brain's mechanisms for motor control and cortical plasticity but also provides a platform on which to further develop neuroengineering strategies to improve mobility and independence.

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