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Question: Can electrophysiological recordings of cone photoreceptors be achieved in wild-type mice?

Background: In the June 2005 issue of Physiology, we highlighted a manuscript from Nikonov et al. that established the Ntr+/ mouse model (null for the neural retina leucine zipper transcription factor), which produces no rods, as a viable option to study cone function. These data provided incontrovertible evidence that Ntr+/ photoreceptors are a species of cones. However, important questions regarding the validity of this model system to study cone physiology were left unanswered. Now, the question of whether wild-type (WT) and Ntr+/ cones have similar functional properties is considered.

Observations: Except for the use of background illumination to isolate the cone responses, the same method to record from Ntr+/ cones was used to achieve, for the first time, electrophysiological recordings on single cones from WT mice, a contention supported by six lines of evidence. The authors also exploited knockout mice lacking the α-subunit of the G-protein transducin, which is required for rod transduction. These WT and knockout mice were utilized in a convincing manner to demonstrate that recordings of cone responses are achievable from many cells. Nikonov et al. present a thorough quantitative analysis of photoresponses under dim light, saturating stimulation, and background illumination.

Significance: Retinitis pigmentosa (RP) is a genetic disorder that causes the degeneration of cells in the retina. First, cones lose their light-sensitive outer segments, and then they die. The current findings are thus of intense interest because of the central role that mouse transgenic lines will play in unraveling cone phototransduction. Mechanistic explorations aimed at further understanding cone physiology will aid in comprehending the pathological processes associated with RP and pharmacotherapies to combat it.


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Question: Can the chronic expression of a single aggregation-prone protein have global effects on cellular homeostasis?

Background: Under normal physiological conditions, improperly folded proteins induce cellular stress responses that elevate the expression of molecular chaperones and proteases, which function to maintain homeostasis of the folding environment. Aggregation-prone proteins cause dysfunction in the normal protein-folding mechanism and the clearance process, which leads to an accumulation of improperly folded proteins. Chronic expression of misfolded and aggregation-prone proteins is a common feature of many protein conformation diseases; however, it is not understood how the presence of a single misfolded protein leads to global cellular dysfunction.

Observations: Using functionally unrelated mutations, Gidalevitz et al. explored the consequences of chronically expressing an aggregation-prone protein on the homeostasis of distinct mutant proteins that are highly sensitive to perturbations of the folding environment. They determined that chronic expression of an aggregation-prone protein could interfere with the normal functions of functionally and structurally unrelated proteins. These unrelated proteins, which harbor mutations that are benign under normal physiological conditions, exacerbated the dysfunctional protein-folding process, via a positive feedback mechanism, when the aggregation-prone protein was present.

Significance: Although several diseases, such as Huntington’s disease, Parkinson’s disease, and Alzheimer’s disease, are linked to mutations that result in the chronic aggregation of proteins, they are usually associated with distinct pathogenic mechanisms. These studies provide new insights into how the chronic expression of a single misfolded protein can perturb the cellular protein-folding mechanism when an aggregation-prone protein is expressed. This suggests that, in the presence of aggregation-prone proteins, failure of the stress response to control protein folding and clearance mechanisms may be a common mechanism that contributes to the pathogenesis of several human diseases.


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Question: What accounts for the fact that a mixture of two odorants elicits odor perceptions that are distinct from the odor perceptions of the individual components?
Background: The odorant receptor (OR) family is responsible for detecting more than 10,000 distinct environmental chemicals in the nose. Each OR recognizes a specific odorant structural feature such that each odorant is detected by a unique combination of ORs. After OR activation, the olfactory sensory neurons in the nose transmit the odor signals to the olfactory bulb (OB) where the signals are segregated into different glomeruli. Those signals are then relayed to olfactory cortex (OC), where inputs from different ORs are targeted to different but spatially overlapping clusters of cortical neurons.

Observations: Zou and Buck compared the induction of an immediate early gene in mouse OC neurons by binary mixtures of odorants versus their individual components, which allowed them to temporally segregate the experiences. They found that use of a binary mixture of odorants resulted in the stimulation of a significant number of cortical neurons that are not stimulated by the individual component odorants.

Significance: Interestingly, these findings are in stark contrast to electrophysiological data collected in the OB, which indicate that most OB relay neurons that respond to an odorant mix also respond to the singular components of that mix. These results suggest that OC neurons act as coincidence detectors, which are only activated by simultaneous inputs from more than one OR. This provides a potential explanation for how mixed odors are perceived as being distinct from their individual components and implies that this experience is due to novel cortical representations of these odors.

Caspase activation contributes to endotoxin-induced diaphragm weakness.

Nominated by Jerry Dempsey
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Question: Is muscle protein loss associated with respiratory muscle weakness?
Background: Respiratory failure can occur as a result of an abnormality in any of several components of the respiratory system, including the respiratory muscles. Respiratory muscle weakness can be induced by even minor infections, with severe infections reducing the generating capacity of these muscles by 80%. There are two mechanistic theories by which infections are postulated to induce respiratory muscle weakness. The first is activation of the proteosomal degradation system that involves cytokine-induced muscle protein loss. The other involves cytokine induction but in the absence of protein loss.

Observations: Because the cytokine caspase-3 induces actin and myosin release, Supinski and Callahan hypothesized that inflammation of the diaphragm would activate caspase-3 and weaken diaphragm force. Their evidence supports this hypothesis. They found that an inflammatory stimulus induced caspase-3-mediated diaphragm weakness in mice and that by blocking caspase-3 activation they could prevent the induced diaphragm weakness. The decrease in diaphragm force occurred without any change in diaphragm muscle content.

Significance: These findings suggest that inflammatory stimuli reduce diaphragm muscle force generation in the absence of diaphragm protein depletion. Not only does this cast doubt on the competing hypothesis that theorizes protein depletion does occur, it also reveals a unique role for caspase-3, which is known to play a role in apoptosis. Therefore, inhibitors of caspase-3 or its upstream activators could potentially be novel therapeutic targets that would mitigate muscle weakness.

Cycling efficiency in humans is related to low UCP3 content and to type I fibres but not to mitochondrial efficiency.

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Question: Can variations in mitochondrial efficiencies account for differences in efficiencies of work performance?
Background: The efficiency of performed work can vary between subjects by as much as 30%. Training is thought to increase work efficiency, and some evidence suggests this occurs by increasing the proportion of type I over type II muscle fibers. However, to fully understand what accounts for this variability, it is necessary to consider that how efficiently physical work is performed depends on how effectively nutrients are converted into energy. Therefore, work efficiency is dependent on the efficiency of the ATP-producing (oxidative phosphorylation) process and the efficiency of converting that ATP into work.

Observations: Using trained and untrained cyclists, Mogensen et al. demonstrated that differences in cycling efficiency were not due to variations in mitochondrial efficiencies as they had hypothesized. Surprisingly, they found that mitochondrial efficiency did not vary between the two subject groups.
Cycling efficiency, however, was correlated to the proportion of type I fibers and to the content of the uncoupling protein isotype 3, which is reduced by training and is lower in type I fibers.

**Significance:** This paper represents an outstanding example of translational research because it links cellular events with a multifactorial and complex phenotypic trait, athletic performance. Thus these data may be of particular interest to elite endurance athletes, because efficiency is a key determinant in their success during competitions. In fact, the October 2005 issue of Physiology highlighted a report that demonstrated an increase in Lance Armstrong’s muscular efficiency over the years was one factor that could be linked to his exceptional performance.

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**Mechanical compression elicits vasodilatation in skeletal muscle feed arteries.**


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**Question:** What causes the rapid vasodilatation of skeletal muscle associated with the onset of exercise?

**Background:** When a muscle contracts during exercise, there is an immediate increase in blood flow (hyperemia). Because this initial dilatation occurs so rapidly, it is unlikely that a metabolite is created and released quickly enough to act on adjacent blood vessels. Previous research has also ruled out the possibility that this is a neural process. However, the walls of vessels respond to mechanical stimuli, such as sheer stress and cyclic stretch; thus vasculature compression during contraction may be the underlying mechanism that induces the exercise-induced hyperemia.

**Observations:** In this paper, Clifford and his team demonstrated in an in vitro preparation that rat feed arteries respond to pulses of external pressure with a similar time course of vasodilatation as observed during brief muscle contractions in humans and animals. Although the magnitude of the dilatation was unaffected by the duration of the compression, it was enhanced by increasing the number of compressions. Moreover, the evidence suggests that the dilatation was mediated by both endothelium-dependent and -independent signaling pathways.

**Significance:** These data provide insight into one of the great physiological puzzles vexing researchers for over a century. They support the theory that extravascular pressure causes deformation of the vasculature within the contracting muscle, leading to the activation of an intrinsic and dynamic mechanosensitive mechanism, which causes the dilatation. Future studies will undoubtedly explore the specific mechanism that underlies this vasodilatation response to vascular compression.

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**Maxi-K channels contribute to urinary potassium excretion in the ROMK-deficient mouse model of type II Bartter’s syndrome and in adaptation to a high potassium diet.**


Nominated by Heini Murer
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**Question:** What accounts for the paradoxically low concentration of K+ in the blood (hypokalemia) of infants afflicted with Bartter’s syndrome?

**Background:** Bartter’s syndrome is clinically characterized by enlargement of juxtaglomerular kidney cells, hypokalemia, alkalosis, renal salt wasting, and increased renin and aldosterone production, factors that are crucial to the maintenance of homeostasis of electrolytes by the kidney. There are five genotypes identified in patients with neonatal Bartter’s syndrome, types I through type V. Type II Bartter’s syndrome results from mutations in the low-conductance K+ channel, ROMK, which recycles K+ in the thick ascending limb of Henle’s loop (TAL) and mediates K+ secretion in the connecting segment and the initial and cortical collecting ducts (CCT). It follows then that infants with type II Bartter’s syndrome are transiently hyperkalaemic, but they unpredictably become hypokalaemic and kaluretic (increased urinary excretion of K+).

**Observations:** Building on the recent discovery that a high-conductance K+ (maxi-K) channel exists in the CCT and the late distal tubule (LDT), Bailey et al. explored the role of maxi-K in the secretion of K+ in ROMK-deficient mice (*Romk−/−*). They determined that reabsorption of K+ in the loop of Henle was inhibited and that maxi-K channels mediated K+ secretion in the LDT. In addition, they found that maxi-K channels also play a major role in the secretion of K+ in wild-type mice fed a high K+ diet.

**Significance:** These studies suggest that ROMK-deficient mice, and by extrapolation infants with type II Bartter’s syndrome, are kaluretic because of reduced reabsorption of K+ in the TAL and because the activation of maxi-K channels allows K+ secretion in the LDT to continue in the absence of ROMK, although at a reduced rate. These results also highlight the importance of maxi-K channels in mediating renal K+ excretion in the LDT in response to high levels of dietary K+ intake.

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**Question:** What accounts for the “loose coupling” of ryanodine receptors (RYRs) and L-type Ca\textsuperscript{2+} channels in smooth muscle?

**Background:** RYRs release Ca\textsuperscript{2+} from the sarcoplasmic reticulum by two mechanisms: spontaneous release (Ca\textsuperscript{2+} sparks) and Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR). CICR occurs in smooth muscle cells and cardiac muscle cells via the type 2 RYR (RYR2), although the features of this induced release is unique between the cell types. In cardiac cells, a small amount of Ca\textsuperscript{2+} entering through the L-type channel is tightly coupled to the release of Ca\textsuperscript{2+} through type II RYRs. By contrast, in many smooth muscle cells, Ca\textsuperscript{2+} sparks occur spontaneously, often from the same sites, triggering transient outward currents that induce hyperpolarization. In some spiking smooth muscle cells, CICR can be activated by the gating of L-type Ca\textsuperscript{2+} channels. Unlike in heart cells, however, the sarcolemmal and sarcoplasmic reticulum channels are “loosely coupled,” meaning that L-type channel gating does not produce obligate Ca\textsuperscript{2+} release, because sufficient Ca\textsuperscript{2+} flux must occur to evoke CICR.

**Observations:** In an effort to elucidate the physiological significance of this loose coupling, Ji et al. determined that RYRs, which are expressed throughout smooth muscle cells, are functional as they were activated by CICR in all areas of the cell. They also found that, when they inhibit expression of the RYR stabilizing protein FK506-binding protein 12.6 (FKBP12.6), the threshold and kinetics of evoked release were altered, providing evidence of the prominent role of RYRs in smooth muscle CICR. Finally, they determined that, at high concentrations of intracellular Ca\textsuperscript{2+}, CICR can also occur through inositol trisphosphate receptors.

**Significance:** This study represents a major contribution toward understanding the molecular processes that underlie excitation-contraction coupling in smooth muscle cells. Not only do they further emphasize the importance of RYRs in CICR, they reveal a novel role of inositol trisphosphate receptors in CICR and provide some insight into the role FKBP12.6 has in determining the Ca\textsuperscript{2+}-induced gating sensitivity of these channels.

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**Question:** Can green tea extract (GTE) increase endurance running capacity?

**Background:** Green tea contains catechins, which are a class of polyphenols that have nutritional and pharmacological properties, such as anti-carcinogen and anti-diabetic effects. Recently, Murase et al. reported that long-term, but not acute, GTE supplementation resulted in an increase in swimming time to exhaustion, which was accompanied by lower respiratory quotients and higher rates of fat oxidation. This report examines whether these effects were conserved in another form of exercise, namely running.

**Observations:** In the current study, Murase and colleagues examined the effects of GTE supplementation on endurance running, whole body energy utilization during running, and the underlying mechanism of GTE-induced lipid metabolism. GTE supplementation was found to improve endurance running, which was associated with an increase in lipid metabolism during exercise. They also provided evidence that the lipid-metabolizing effect of GTE supplementation was due to a decrease in muscle levels of malonyl-CoA, which disinhibits fatty-acid metabolism.

**Significance:** The results indicate that GTE is beneficial for improving endurance capacity and support the hypothesis that the stimulation of fatty acid utilization is a promising strategy for improving endurance capacity. Although the clinical efficacy of GTE has not been demonstrated, these results suggest that GTE may be a viable pharmacological approach for improving endurance capacity in humans.

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**Question:** What is the molecular mechanism that promotes activity-dependent myelination by mature oligodendrocytes?

**Background:** Oligodendrocytes are a type of neuroglia that surrounds and insulates axons to maintain the propagation of action potentials. Recent evidence suggests that the myelination process is positively regulated by action potential firing. Although some of the
molecular details that govern the early stages of activity-dependent myelination are known, the molecular mechanism(s) that underlie the later stages of activity-dependent myelination have not been empirically explored.

**Observations:** Ishibashi et al. determined that electrical stimulation induces an increase in the myelination of mature oligodendrocytes via an ATP-dependent mechanism. The release of ATP promoted myelination by increasing the cytokine leukemia inhibitory factor (LIF). Interestingly, this phenomenon did not occur directly on oligodendrocytes; rather, electrical stimulation indirectly induced oligodendrocyte-mediated myelination by stimulating ATP-induced LIF release from astrocytes. Finally, LIF affected myelination in a biphasic manner, increasing it at low concentrations and inhibiting it at high concentrations.

**Significance:** Multiple sclerosis (MS) is an inflammatory disease of the central nervous system that is clinically characterized by a loss of myelin. This work may provide greater insight into the pathophysiology of MS as it delineates links between electrical activity, astrocytes, ATP, LIF, and the late stages of oligodendrocyte-induced myelination. Finally, the reported biphasic effect of LIF on myelination is interesting because it explains discrepancies previously reported in the literature concerning the effect of LIF on myelination.