The United States are fortunate that science has come to the rescue of the country. The scientific community has come together to face the pandemic with hard work, ingenuity, and the power of the scientific method. The stimulus funds have been directed towards technologies that will stimulate the economy and hard work, which will ensure that the country comes out stronger than ever. It is up to the current administration to ensure that the stimulus funds are used effectively and efficiently.

**Significance:** These findings suggest that, in an experimental design that more closely resembles physiological conditions, the force fatigue arises through the action of actin and myosin cross-bridge cycling and thus the accumulation of metabolites. Indeed, their finding that fatigue is less at high temperatures than at low temperatures is consistent with the idea that accumulation of products of ATP hydrolysis is the main cause of fatigue. Although earlier studies have reported faster fatigue at higher temperatures using different experimental conditions, the authors suggest that the sensitivity of force production to metabolites decreases as temperature increases. Additional experiments will be required to sort this out. Nonetheless, this report adds a valuable step toward elucidating the underlying molecular mechanisms that cause deterioration of muscle performance under normal physiological conditions.

**Question:** What causes muscle fatigue? How does temperature affect these results?

**Background:** When muscles are activated by motorneurons, they respond by generating tension in the muscle fibers. This process requires the hydrolysis of ATP, which results in an accumulation of metabolic products. The accumulation of metabolic products is a primary factor associated with a decline in muscle force (fatigue). The mechanisms involved in fatigue have been studied using a variety of intensities, durations, and variations in the mechanics of the contractions involved, but they have typically been performed under artificial conditions, such as at room temperature.

**Observations:** In these experiments, Roots et al. utilized isolated, small bundles of fast fibers from rat muscle and looked at their performance at a range of temperatures. Additionally, they used shortening contractions instead of isometric contractions, which do not show the same temporal decline in force as is associated with myofibrillar fatigue. One interesting finding was that in shortening mode (i.e., when the muscle shortened during part of the contraction) the fatigue of force was greater than in isometric mode. In addition, and perhaps surprisingly, they found that, as the temperature increased, the extent of fatigue decreased.

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**Intracellular sodium regulates proteolytic activation of the epithelial sodium channel.**


**MicroRNAs (miRNAs) are noncoding RNAs that are complementary in part, to messenger RNAs (mRNAs). As such, miRNAs regulate genes and biological pathways via posttranscriptional mechanisms that control the expression of mRNAs and/or proteins.**
Significance: These results suggest that miR-21 plays a major role in regulating a stress-response pathway associated with cardiac failure. Perhaps more importantly, these findings suggest that targeting miRNAs as potential therapeutic targets for cardiac diseases is worthy of further investigation. In fact, this is the first study to demonstrate the therapeutic efficacy of antagonizing a single miRNA and correcting an entire disease pathway. This approach holds promise not only for cardiac diseases but provides a new approach for innovative medicines for other disease areas based on miRNAs, where the interruption of entire disease pathways can be achieved.

Critical role of transcription factor cyclic AMP response element modulator in beta(1)-adrenoceptor-mediated cardiac dysfunction. Lewin G, Matus M, Basu A, Frebel K, Rohsbach SP, Safronenko A, Seidl MD, Stumpfl F, Buchwalow I, König Frebel K, Rohsbach SP, Safronenko A, Lewin et al. employed transfection to study these factors in cardiac tissue. They found that CREM inactivation in beta1AR-overexpressing mice, it had a protective effect on cardiomyocyte hypertrophy, fibrosis, and ventricular dysfunction. Interestingly, several genes previously associated with differential expression of beta1ARs were not affected. However, expressions of several myocardial proteins, such as the cardiac ryanodine receptor, were altered in this mouse line. 

Significance: These morphological, functional, and expression findings suggest that the altered regulation of CREM-induced gene expression may contribute to detrimental beta1AR-mediated cardiac effects. Additionally, several genes that encode functionally important contractile proteins are implicated as having an essential role in cardiac physiology and the pathogenesis of heart failure. As such, directly modulating CREM may prove to be a useful target of drugs aimed at decreasing mortality in human heart failure.


Observation: Using obese animal models including db/db and ob/ob mice, Kim et al. determined that BBR increased energy expenditure, although it also selectively decreased fat mass in the obese subjects as well. Nonetheless, they went on to find that BBR exposure resulted in mitigation of hepatic structural changes, decreased enzyme levels typical of liver damage, and alterations in the expressions levels of genes involved in lipid metabolism: effects mediating by both central and peripheral AMPK. They conclude by blocking the prophylactic effects of BBR through AMPK inhibition. These findings extend previous reports by implicating AMPK in the inability of BBR to stimulate fatty acid oxidation and reverse fatty liver associated with obesity. Although BBR has been used for thousands of years in China for the treatment of diseases, including diabetes, these findings provide an understanding of the mechanism that underlies this phenomenon. As such, given that BBR mediates these effects via peripheral and central AMPK regulation, more selective drugs are likely to follow to mitigate unwanted side-effects or isolate the anti-diabetic and anti-obesity effects.


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HIGHLIGHTS FROM THE LITERATURE

CFTR functions as a bicarbonate channel in pancreatic duct cells. Ishiguro et al. measured voltage-driven fluxes of HCO3– permeability from voltage-driven secretion across apical membranes of pancreatic duct cells and have significant implications for future treatment of CF.


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Under normal physiological conditions, the pancreas aids in the digestive process by secreting an alkaline pancreatic juice that contains enzymes, which are passed to the small intestine. The molecular mechanisms of bicarbonate uptake across basolateral membranes of pancreatic duct cells are well defined, however, the same cannot be said about bicarbonate transport across the apical membrane. It is known that the CFTR is situated in the apical membrane of pancreatic duct cells and if CFTR function is compromised, ductal bicarbonate secretion is impaired. Hence, CFTR is known to be necessary for secretion, but the exact role of CFTR is not well defined.

Observations: Ishiguro et al. measured voltage-driven fluxes of HCO3– through conductive pathways in the apical membrane of pancreatic duct cells. After blocking alternative pathways, they were able to estimate apical HCO3– permeability from voltage-driven changes in intracellular pH. They also showed that these changes were stimulated by cAMP and occurred independently of the presence of Cl– and luminal Na+. In addition, pharmacologically blocking CFTR and genetically mutating CFTR so that it was not functional significantly attenuated HCO3– flux. The authors conclude that CFTR, functioning as a HCO3– channel in pancreatic duct cells, makes a significant contribution to HCO3– secretion.

Significance: This is the probably first study to estimate absolute HCO3– permeability in native epithelium. It has been known for some time that the ratio between alkaline fluid and secreted digestive enzymes is significantly decreased in patients with cystic fibrosis (CF) and that HCO3– secretion is impaired. The present results provide an important new insight into the mechanism of HCO3– secretion across apical membranes of pancreatic duct cells and have significant implications for future treatment of CF.

Background: Using liquid chromatography mass spectrometry (LC-MS)-based metabolomics, Nelson and colleagues measured differences in small molecules in five different states of varying activity associated with hibernation in squirrel liver. They determined that there were seasonal and torpor-arousal cycle alterations in several metabolic processes that coincided with arousal levels.

Significance: Using a novel, discovery-based approach to characterize the changes in small molecules in ground squirrels, these findings highlight the value of metabolic analyses in determining the different phenotypes associated with hibernation. In addition to discovering novel physiological and molecular changes associated with hibernation, the Carey group aims to translate insights gained from the hibernation phenotype to improvements in human and animal biomedicine.

Question: Does the heart have two pacemakers?

Background: The sinoatrial node cells (SANC) of the heart create rhythmic impulses that then spread throughout the heart. This pacemaker activity has been widely attributed to sarcolemmal channels, but evidence of a subcellular oscillator that could work independently of the sarcrolemma has existed for decades. However, since recording methods were not capable of measuring these oscillations, they were largely ignored until recently. With the emergence of more precise techniques, the idea that pacemaker activity also involves time-dependent release of Ca2+ from the sarcoplastic reticum (SR) is clear. What has not been reconciled is the coupling of the membrane voltage oscillator with the internal SR Ca2+ oscillator in normal SANC function.

Observations: Maltsev and Lakatta develop a numerical model of the oscillatory activity of the SANCs that includes both the classical sarcolemminal ion channel oscillator and the internal Ca2+ oscillator. When the oscillator systems are coupled, they observed that pacemaker activity involves both the membrane oscillator and the Ca2+ oscillations. They also found greater robustness and flexibility when the two were coupled than when the membrane clock was operating alone. Moreover, their modeling predicts that blocking the intracellular Ca2+ clock has a major effect on the rate and rhythm of oscillations of the pacemaker system.

Significance: This is the first model of pacemaker activity that includes the internal Ca2+ clock. Thus novel theories of heart contraction and rhythm will emerge that include this component, which may have some effect on the age-related decrease in SAN function. As such, this model may be useful for developing novel therapies to treat pacemaker abnormalities and arrhythmias.