IN THIS ISSUE

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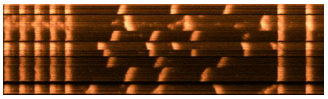
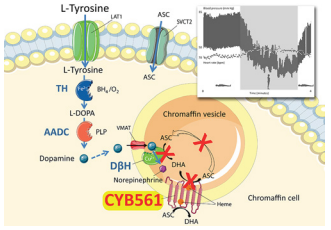


JNK2/CaMKII Crosstalk Underlies Atrial Arrhythmias (p 821)

Inhibiting JNK2 reduces the risk of atrial fibrillation, report *Yan* et al.

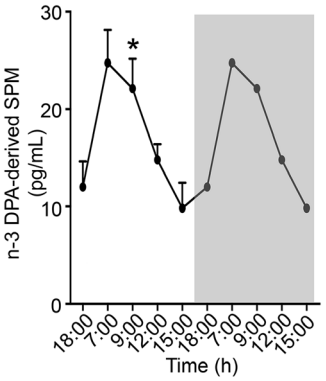
Characterized by a rapid and irregular heartbeat, atrial fibrillation (A-Fib) is associated with hypertrophy, heart failure, ischemia, and old age. Indeed, between 10 and 15% of 70- to 80-year olds develop A-Fib. However, in addition to A-Fib, the activity of the stress–response enzyme c-Jun N-terminal kinase (JNK) also increases with age, hypertrophy, heart failure, and ischemia, which prompted Yan and colleagues to investigate whether A-Fib and JNK share a more direct link. Focusing on JNK2, which is the major JNK isoform in the heart, the team confirmed that the activity of the enzyme is positively correlated with age in both human and mouse hearts. They then showed that elevating JNK2 activity in young mice caused abnormal intracellular calcium handling in the heart, and that JNK2 phosphorylated and activated the protein kinase CamKII, a known driver of arrhythmia. Moreover, inhibition of JNK2 in older animals prevented CamKII activation, aberrant calcium handling, and, most importantly, A-Fib susceptibility. As JNK2 inhibitors are currently under clinical investigation for the treatment of cancer and arthritis, these inhibitors may be attractive candidates for preventing or treating A-Fib.



CYB561 and Orthostatic Hypotension (p 846)

van den Berg et al discover a new mutation underlying orthostatic hypotension.

Orthostatic hypotension—a sudden drop in blood pressure upon standing after lying or sitting—can cause dizziness, fainting, and even loss of consciousness. Although mild or occasional cases are common, in some people, the condition can be severe enough to be life-threatening. Some individuals with mutations in the enzyme dopamine β-hydroxylase (DβH), for example, have impaired production of the catecholamines, norepinephrine and epinephrine, and, as a result, dangerously low blood pressure. Now, van den Berg and colleagues have uncovered a new genetic cause of orthostatic hypotension. They found that 4 patients (2 sets of sisters) with severe, life-long illness and with catecholamine levels indicative of DβH deficiency, did not in fact have DβH mutations or reduced DβH activity. Instead, genetic analysis, including whole-exome sequencing, revealed that the women had homozygous mutations in the gene encoding cytochrome b561 (CYB561)—a transmembrane electron transporter. Investigations into the functional consequences showed that these mutations perturbed electron shuttling necessary for norephinephrine synthesis. Encouragingly, treatment with the norephinerine precursor L-dihydroxyphenylserine, while producing unpleasant side effects, increased blood pressure and relieved symptoms in all 4 patients.



Vascular $RvD_{n\text{-}3\ DPA}$ Reduce Systemic Inflammation (p 855)

$RvD_{n\text{-}3\ DPA}$ tempers the daily increase in leukocyte and platelet activation, report *Colas* et al.

Specialized proresolving mediators (SPMs) are recently identified molecules that promote the resolution of inflammation. Armed with the knowledge that inflammation naturally waxes and wanes at different periods of night and day, Colas and colleagues investigated whether SPM levels might also exhibit diurnal variation. They found that blood obtained from healthy volunteers at regular intervals over a 24-hour period had higher level of the SPM $RvD_{n\text{-}3\ DPA}$ at night and that these levels dropped in the morning, coincident with increased leukocyte activation. Moreover, incubation of whole blood with $RvD_{n\text{-}3\ DPA}$ caused a decrease in neutrophil, platelet, and monocyte activation. Because such leukocyte and platelet activation are linked with cardiovascular disease (CVD)—and to increased occurrence of adverse cardiovascular events in the morning—the team measured $RvD_{n\text{-}3\ DPA}$ in patients with CVD. They found that, compared with healthy controls, people with CVD had lower levels of $RvD_{n\text{-}3\ DPA}$ and that the diurnal regulation of the SPM $RvD_{n\text{-}3\ DPA}$ was impaired. Taken together, these findings suggest that $RvD_{n\text{-}3\ DPA}$ moderates the diurnal elevations in leukocyte activation and that loss of this regulation may lead to CVD.

Written by Ruth Williams

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