From the Literature

Tracy Hampton, PhD

Researchers Identify Multiple Backups to Heart's Pacemaker

A new study sheds light on how the human sinoatrial node (SAN) efficiently maintains heart rhythm even under adverse conditions. The findings could help improve treatments for cardiac arrhythmias.

"Our most important finding was that the human SAN is hardwired with a backup system: 3 diverse regions of intranodal pacemakers acting as batteries and up to 5 conduction pathways that act as wires to connect the electric signal to the atria," said Vadim Fedorov, PhD, senior author of the *Science Translational Medicine* study.[1]

For the research, Dr Fedorov, of The Ohio State University Wexner Medical Center, and his colleagues combined optical mapping, 3-dimensional tissue reconstruction, and molecular characterizations to create an integrated picture of the SAN in action in donated human hearts that were not viable for transplantation. The researchers placed each heart in a glass chamber and perfused the coronary arteries with an oxygenated solution that simulates blood flow, allowing the SAN to beat with the same rhythm as when it was inside the body. The chamber was then surrounded by infrared cameras, and a fluorescent dye was injected to allow the scientists to visualize spontaneous electric activity moving within the human SAN in 3 dimensions.

Researchers show that human sinoatrial node efficiently maintains heart rhythm even under adverse conditions. Results contribute to the development of novel clinical therapies such as fail-safe biological pacemakers.

When the investigators disrupted SAN function with adenosine or atrial pacing, redundant intranodal pacemakers were able to compensate, ensuring a fail-safe mechanism to maintain automaticity and deliver electric impulses to the atria through sinoatrial conduction pathways.

Molecular analyses revealed substantial differences in the abundance of certain proteins in different areas of the SAN, potentially allowing those regions to avoid disruption during challenges that would otherwise halt the heartbeat.

The results may contribute to the development of novel clinical therapies such as fail-safe biological pacemakers. "Our study is providing the foundation for seeking out ways to improve or restore SAN function in patients with impaired SAN and thus avoiding electronic pacemaker implants," said Dr Fedorov. "Our hope is that someday, electronic pacemaker implants could be obsolete."

Li N et al. Redundant and diverse intranodal pacemakers and conduction pathways protect the human sinoatrial node from failure. *Sci Transl Med*. 2017;9:eaam5607. doi: 10.1126/scitranslmed.aam5607.

Inactivating the "Hunger Hormone" May Prevent Postdiet Weight Gain

Calorie restriction can successfully lower body weight, but dieters typically regain weight because of compensatory hormonal and metabolic changes. New research published in the *Proceedings of the National Academy of Sciences of the United States of America* suggests that targeting the appetite-stimulating hormone ghrelin may be an effective strategy to help keep the weight off long-term. This "hunger hormone" rises shortly before a meal and falls

afterward, and studies have found that obesity promotes ghrelin resistance, whereas dieting and weight loss increase the sensitivity of the ghrelin receptor.

To mimic dieting in overweight and obese individuals, investigators at the Mayo Clinic in Rochester, MN fed mice from 8 to 20 weeks of age a high-fat diet before switching them to a diet with 40% lower calorie content than their previous diet, leading to substantial weight loss. When the mice were switched to the calorie-restricted diet, they were also injected with an adeno-associated virus expressing either the enzyme butyrylcholinesterase (BChE), which inactivates ghrelin, or a control enzyme, luciferase. After 3 weeks on the restricted diet, mice were then fed an unrestricted low-fat diet.

Following the end of the restricted diet, mice treated with the single injection of the BChE vector expressed lifelong high plasma levels of BChE and lower levels of acyl-ghrelin, the active form of ghrelin, than the control-treated mice. BChE gene transfer also resensitized ghrelin receptors.

It is important to note that BChE-treated mice consumed fewer calories, regained less weight, and had better glucose tolerance than control-treated mice. Spontaneous activity and energy expenditure did not differ significantly between the groups of mice after body weight rebound.

Other investigators have targeted aspects of ghrelin biology to develop potential therapies for obesity and related diseases. This latest study's finding that a single injection had lifelong effects in mice makes the strategy of BChE treatment in combination with calorie restriction especially promising.

Previous work by this team found that BChE can also cause cocaine to be metabolized quickly, reducing the drug's reward. "At present we are focusing our efforts on rigorous pathology and toxicity studies and preparing a case to the US Food and Drug Administration that this approach to treating drug addiction and rebound obesity will be safe and efficacious," said senior author Stephen Brimijoin, PhD.

Chen VP et al. Butyrylcholinesterase gene transfer in obese mice prevents postdieting body weight rebound by suppressing ghrelin signaling. *Proc Natl Acad Sci USA*. 2017;114:10960–10965. doi: 10.1073/pnas.1706517114.

Congenital Heart Disease Genes Uncovered

A new study sheds light on some of the underlying genetic causes of congenital heart disease (CHD), and the long-term prognosis for individuals who carry these mutations, as well.

The *Nature Genetics* study, which was conducted by the National Heart, Lung, and Blood Institute Pediatric Cardiac Genomics Consortium, leveraged clinical and genetic data from 2871 patients with CHD, and information and genetic data from parents, as well.

The team found that some genetic mutations are transmitted from parents to children; for example, mutations in the FLT4 gene consistently led to a condition known as tetralogy of Fallot, a complex malformation that often presents with cyanosis, or blue baby syndrome. Also, mutations in the gene that codes for MYH6 (myosin heavy chain 6) accounted for ≈11% of Shone syndrome, which affects regions of the left side of the heart. Some patients with CHD also carried a founder mutation associated with Ashkenazim ancestry: the mutation in both copies of the *GDF1* gene accounted for ≈5% of severe CHD among children of Ashkenazim descent.

The analyses also revealed that some mutations appear for the first time in a child's genome. Such de novo mutations were especially common in genes involved with the modification of chromatin that surrounds DNA. De novo mutations in ≈440 genes were inferred to contribute to CHD, and the researchers found striking overlap between genes with damaging de novo mutations in infants with CHD and autism.

The findings could be useful for expanding genetic testing panels for CHD and to provide information for parents about the recurrence risks in future children and the long-term care of children with CHD.

"It is hoped that understanding the cause of each individual patient's CHD will guide medical and surgical management to optimize outcome. In particular, early identification of patients with a mutation that places them at risk for neurodevelopmental disorders including autism optimizes the chance of successful early developmental interventions," said senior author Martina Brueckner, MD, of the Yale University School of Medicine. "In addition, identification of a specific genetic cause for patients with CHD enables better counseling of families affected by CHD regarding recurrence risks. Hopefully these studies will eventually lead to personalized medicine for congenital heart disease."

Jin SC et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat Genet*. 2017;49:1593–1601. doi: 10.1038/ng.3970.

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