takefuji@med.nagoya-u.ac.jp

alon_chen@psych.mpg.de Max Planck Institute of Psychiatry

The information provided in this document has been prepared for discussion purposes based on the application of epigenetics to cardiac and vascular issues.

As explained in the website www.MCFIP.net, epigenetics based on physical science establishes a new discipline that will allow research to identify the causes of chronic diseases. With that said, unless interested parties are willing to allocate the time to understand epigenetics, they should not attempt to try to decipher the findings of our twelve year process. However, MCFIP has the ability to share its findings on a time available basis with a limited number of entities that are seeking to apply and commercialize the epigenome.

++

Relative to the following article, CRCR2 is a receptor that can be activated by the epigenetic cell surface signaling molecule UNC2.

The first step in epigenetic modeling is to set aside assumptions by researchers that they understand epigenetics. For example, the following explains how cell surface signaling molecules are formed:

http://www.mcfip.net/upload/Cell%20Surface%20Signaling%20Molecule%20Formation.pdf

Using an array of epigenetic modeling tools, over the past decade, a large data base of epigenetic signaling molecules has been amassed based on minerals/elements and amino acid constituents. This process allows for comparisons that can prevent duplications and, with meta-analysis, provide the opportunity to identify likely causes of chronic

diseases based on “roles” for common signaling despite varying designations.

When subjected to epigenetic modeling based on physical science that can be verified, the following were outcomes for urocortin 2.

- It is one of three members of the UNC “family” - UNC1 - 3
- As identified in the 2011 document affixed to this article, UNCs are derived from corticotropin-releasing factor (CRF). Our modeling can establish CRF to be bioidentical to corticotropin-releasing hormone (CRH); i.e. same substance with different nomenclature.
- Three forms of CRH exist; CRH1- CRH-2 and CRH-3
- They are byproducts of the iron - sulfur based pancreatic polypeptide (PP); aka IL-16 and aldosterone.
- Aldosterone can be verified as being the neurohormone that is responsible for fear - anxiety and the driver for hypertension. **http://www.mcfip.net/upload/Aldosterone%20-%20Hypertension%20-%20Confirmation.pdf**
- The amino acid constituents of the byproducts of iron - sulfur based cytokines that form the UNC cell surface signaling molecules are phenylalanine - tyrosine - tryptophan.

Summary

We have opted to provide an introductory overview of the epigenetic variables associated with neuropeptides and neurohormones. Details for the epigenome are far too complex for presentation via written documents. Accordingly, interested entities are encouraged to contact MCFIP to discuss the ways to gain access to the epigenome modeling tools and data.

Scientists identify protein linked to chronic heart failure

May 26, 2017

Researchers in Japan have identified a receptor protein on the surface of heart cells that promotes chronic heart failure. The study, "Corticotropin releasing hormone receptor 2 exacerbates chronic cardiac dysfunction," which will be published May 26 in *The Journal of Experimental Medicine*, suggests that inhibiting this protein could help treat a disease that affects more than 20 million people worldwide.

Chronic heart failure is caused by a variety of conditions that damage the heart, including coronary heart disease, hypertension, and diabetes. Although the heart initially tries to compensate for this damage and maintain its function by, for example, growing larger, cardiac function gradually declines until the heart is no longer able to pump enough blood and oxygen around the body. According to the CDC, about 5.7 million adults in the US have heart failure, and around half of these patients die within 5 years of their initial diagnosis. Indeed, heart failure contributes to as many as one in nine deaths across the country. MCFIP - For discussion purposed, the information provided in this document established the verifiable epigenetic modeling that explains how neurohormone imbalances are a prime factor for heart failure.
Note: The website www.MCFIP.net has been developed to provide open access to epigenetic modeling. The following is also provided for use as part of discussions for cardiovascular issues that are related to the epigenome.
http://www.mcfip.net/upload/Epigenetic%20Examples%20-%20Vascular%20Issues%20x.pdf

A team of researchers led by Mikito Takefuji from Nagoya University School of Medicine discovered that a signaling protein called corticotropin releasing hormone receptor 2 (Crhr2) is expressed on the surface of heart muscle cells, or cardiomyocytes, and that Crhr2 levels increase in mice suffering from heart failure.

Crhr2 is a G protein-coupled receptor whose ability to alter cardiomyocyte function is activated by a protein called urocortin 2 (Ucn2). Ucn2 levels were elevated in the blood of both mice and human patients with chronic heart failure, the researchers found. Sustained treatment of otherwise healthy mice with Ucn2 was sufficient to reduce cardiac function.

Takefuji and colleagues found that the activation of Crhr2 by Ucn2 stimulates several downstream signaling pathways that result in the expression of genes that impair heart function. Mice lacking Crhr2 were protected from the effects of Ucn2 and were resistant to developing heart failure. A small molecule that inhibits Crhr2 was similarly effective in maintaining cardiac function after damage to the heart.

G protein-coupled receptors such as Crhr2 are considered to be relatively easy to target with specific drugs. "Our results suggest that constitutive Crhr2 activation causes cardiac dysfunction and that Crhr2 blockade could be a promising therapeutic strategy for patients with chronic heart failure," Takefuji says.

Explore further: Discovery and gene therapy treatment of a novel heart failure mechanism

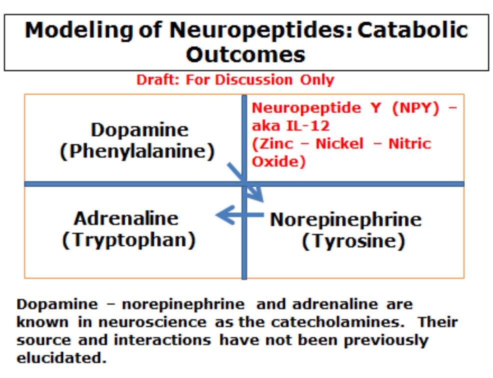
More information: Tsuda et al., 2017. *J. Exp. Med*. **jem.rupress.org/cgi/doi/10.1084/jem.20161924**

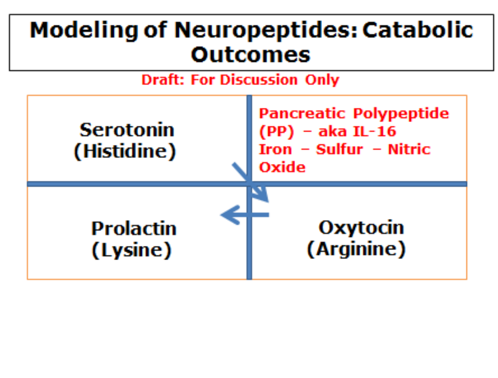
Journal reference: Journal of Experimental Medicine

Read more at: https://medicalxpress.com/news/2017-05-scientists-protein-linked-chronic-heart.html#jCp

Turning Off Stress

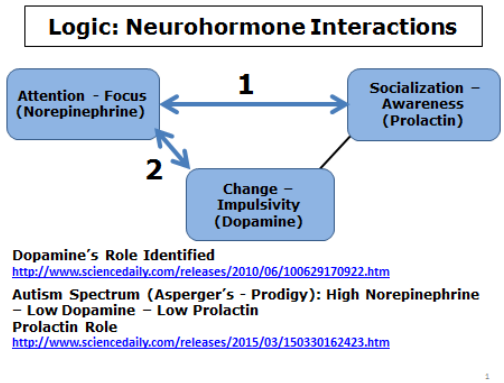
ScienceDaily (Feb. 8, 2011) — Post-traumatic stress disorder can affect soldiers after combat or ordinary people who have undergone harrowing experiences. Of course, feelings of anxiety are normal and even desirable -- they are part of what helps us survive in a world of real threats. But no less crucial is the return to normal -- the slowing of the heartbeat and relaxation of tension -- after the threat has passed. People who have a hard time "turning off" their stress response are candidates for post-traumatic stress syndrome, as well as anorexia, anxiety disorders and depression. MCFIP - Neurohormone byproducts of the neuropeptides NPY and PP can be verified as being the sources from which the neurohormones for logic and emotions are formed by catabolic activity. Refer to the following for use as part of discussions:

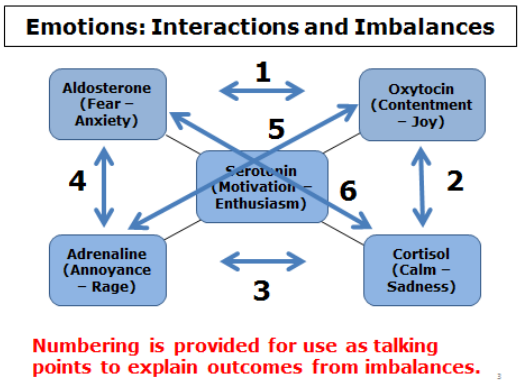




NPY and PP can be verified as being cortisol and aldosterone respectively.

The roles and interactions of the neurohormones can be verified as follows:





How does the body recover from responding to shock or acute stress? This question is at the heart of research conducted by Dr. Alon Chen of the Institute's Neurobiology Department. The response to stress begins in the brain, and Chen concentrates on a family of proteins that play a prominent role in regulating this mechanism. One protein in the family -- CRF -- is known to initiate a chain of events that occurs when we cope with pressure, and scientists have hypothesized that other members of the family are involved in shutting down that chain. In research that appeared in the *Proceedings of the National Academy of Sciences* (PNAS), Chen and his team have now, for the first time, provided sound evidence that three family members known as urocortin 1, 2 and 3 -- are responsible for turning off the stress response. MCFIP – These signaling molecules are also known as corticotropin-releasing hormone 1 - 2 and 3 (CRH1-3).

The research group, including Adi Neufeld Cohen, Dr. Michael Tsoory, Dmitriy Getselter, and Shosh Gil, created genetically engineered mice that don't produce the three urocortin proteins. Before they were exposed to stress, these mice acted just like the control mice, showing no unusual anxiety. When the scientists stressed the mice, both groups reacted in the same way, showing clear signs of distress. Differences between the groups only appeared when they were checked 24 hours after the stressful episode: While the control mice had returned to their normal behavior, appearing to have recovered completely from the shock, the engineered mice were still showing the same levels of anxiety the scientists had observed immediately following their exposure to the stress.

Clearly, the urocortin proteins are crucial for returning to normal, but how, exactly, do they do this? To identify the mechanism for the proteins' activity, Chen and his team tested both groups of mice for expression levels of a number of genes known to be involved in the stress response. They found that gene expression levels remained constant during and after stress in the engineered mice, whereas patterns of gene expression in the control mice had changed quite a bit 24 hours after the fact. In other words, without the urocortin system, the "return to normal" program couldn't be activated.

Chen: "Our findings imply that the urocortin system plays a central role in regulating stress responses, and this may have implications for such diseases as anxiety disorders, depression and anorexia. The genetically engineered mice we created could be effective research models for these diseases."

Dr. Alon Chen's research is supported by the Nella and Leon Benoziyo Center for Neurosciences; the Nella and Leon Benoziyo Center for Neurological Diseases; the Carl and Micaela Einhorn-Dominic Brain Research Institute; the Irwin Green Alzheimer's Research Fund; the Mark Besen and the Pratt Foundation, Australia; the Roberto and Renata Ruhman, Brazil; and Martine Turcotte, Canada. Dr. Chen is the incumbent of the Philip Harris and Gerald Ronson Career Development Chair.

Story Source:

The above story is reprinted (with editorial adaptations by Science*Daily* staff) from materials provided by **Weizmann Institute of Science**.

Journal Reference:

1. A. Neufeld-Cohen, M. M. Tsoory, A. K. Evans, D. Getselter, S. Gil, C. A. Lowry, W. W. Vale, A. Chen. **A triple urocortin knockout mouse model reveals an essential role for urocortins in stress recovery**. *Proceedings of the National Academy of Sciences*, 2010; 107 (44): 19020 DOI: 10.1073/pnas.1013761107

http://www.sciencedaily.com/releases/2011/02/110208101316.htm