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The Problem

When the human body senses a threat, be it real or perceived, our physiology shifts to a defensive mode orchestrated by the brain—the immune system and appetite ramp down, metabolism is altered to liberate fuels, and blood flow is redirected to deliver these fuels to muscles that need them. In the short term, these changes help prepare the body for coping with the emergency at hand. But if this defensive mode is sustained, these same stress-related adaptations can contribute to a wide range of disease states, including pathologies of the central nervous system, such as dementia and multiple sclerosis. To find new ways of keeping stress from worsening disease, researchers need to understand how the stress response machinery works in the first place.

The Approach

Paul Sawchenko uses cell biological and genetic approaches in rodent models to study how stress-responsive systems are organized at a molecular level within the body and particularly within the brain. His work seeks to identify how different kinds of stressful information reach the brain and to unravel the pathways and molecules involved in conveying this information to brain centers. Knowledge of this basic wiring diagram, and particularly of the molecules that govern the flow of information within it, helps identify drug targets that could combat the wide range of stress-related neurological diseases in a more effective and informed manner.

The Innovations and Discoveries

- Sawchenko showed that a receptor for the stress hormone, corticotropin-releasing factor (CRF), is directly involved in modifying certain brain proteins in such a way as to contribute to the development of plaques and tangles, the two defining neuropathological hallmarks of Alzheimer's disease. Drugs that block signaling through this CRF receptor reduce brain damage and deficits in learning and memory in a mouse model of Alzheimer's, suggesting a new potential treatment for this devastating disease.

- Sawchenko and colleagues discovered a novel anti-inflammatory signaling mechanism within the brain's blood vessels. The lab is working to harness this mechanism to improve the clinical outcome in animal models of the many neurodegenerative disorders that have an inflammatory component, including ALS, Alzheimer's and Parkinson's diseases.

- Sawchenko's lab also aims to unravel brain circuitry related to past experience, emotion and stress in the hopes of better understanding a range of psychiatric disorders, including depression and post-traumatic stress disorder (PTSD).

For more information, please visit:
http://www.salk.edu/faculty/sawchenko.html

Aging, Dementia, Autoimmune Disease, Neurological Disease, Inflammation, Immunology, Neurobiology, Therapeutics