functionally connected supports the idea that hypocretin neurons use glutamate as a fast amino acid transmitter.

Using similar methods, the authors show that the neurotransmitters norepinephine and serotonin, also involved in the regulation of arousal, are connected to this system by another feedback loop with substantial inhibitory action. Hypocretin neurons possess inhibitory receptors for both norepinephine and serotonin. Given the direct stimulating effect of hypocretin on norepinephine cells in the locus coeruleus and serotonin cells in the dorsal raphe, this constitutes a negative feedback loop within the arousal system. Thus, levels of arousal might be regulated by the balanced action of positive (glutamatergic) and negative (noradrenergic and serotonergic) feedback loops. At any point, input from other sources (including metabolic cues such as insulin, glucose, leptin or starvation) can also be integrated. For example, γ-aminobutyric acid reduces the activity of hypocretin cells[3]. Such feedback loops may be dispersed among the other components of the complex sleep-wake system, enabling the system to react to external and internal stimuli in a coordinated fashion.

Li *et al.* have substantially increased our knowledge of complex feedback circuits that regulate arousal in the central nervous system. Will patients with excessive daytime sleepiness or insomnia profit from that? Many drugs used to promote sleep or wakefulness act primarily through single transmitter pathways such as γ-aminobutyric acid or norepinephrine. The authors' data suggest that these drugs may exert their action at least partially by modulating the activity of the hypocretin system, which would explain the similar effect of very different drugs on sleep. These very basic findings should stimulate further clinical research on this system of sleep-wake regulation. Manipulation of hypocretin transmission could be the basis for promising interventions, including the development of hypocretin agonists for narcolepsy and antagonists for insomnia.

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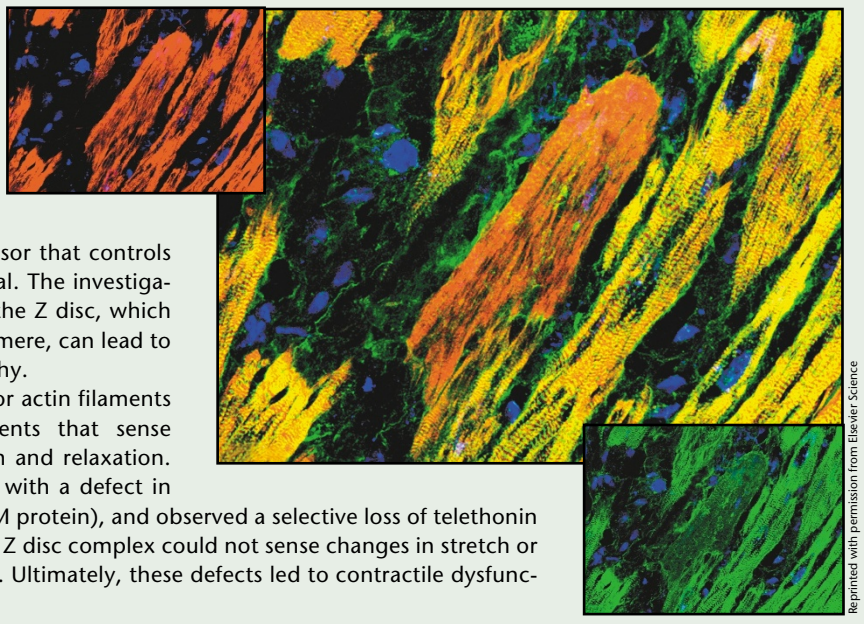
Department of Psychiatry and Psychotherapy
University of Regensburg
Regensburg, Germany
Email: goeran.hajak@bkr-regensburg.de

Stress in the sarcomere



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Excess mechanical stress on cardiac muscle cells can lead to dilated cardiomyopathy, a type of heart failure where an enlarged heart loses its ability to pump blood. In the December 27 *Cell*, Ralph Knöll, Masahiko Hoshijima and colleagues pinpoint the major components of the mechanical sensor that controls normal cardiac muscle growth and survival. The investigators describe how cytoskeletal defects in the Z disc, which defines the lateral boundaries of the sarcomere, can lead to an inherited form of dilated cardiomyopathy.

The Z disc serves as an anchoring site for actin filaments (red) and telethonin (green), components that sense stretch during normal cardiac contraction and relaxation. The authors investigated a mouse model with a defect in the Z disc protein MLP (muscle-specific LIM protein), and observed a selective loss of telethonin (merged). In mice with defective MLP, the Z disc complex could not sense changes in stretch or trigger critical growth and survival signals. Ultimately, these defects led to contractile dysfunction and dilated cardiomyopathy.

The study also identified a group of humans with mutations in the *MLP* gene. Using genetic fingerprinting techniques to test 526 Germans with dilated cardiomyopathy, the investigators identified ten individuals with identical *MLP* mutations. However, no cases of mutant *MLP* were found in 285 Japanese patients. The researchers also identified mutant *MLP* in cardiomyopathy patients of Northern European descent from England, France and the United States, indicating that this mutation has been passed down through several generations of Northern Europeans.

USHMA SAVLA