6. **PROTECTIVE AND DAMAGING EFFECTS OF STRESS MEDIATORS: ALLOSTASIS AND ALLOSTATIC OVERLOAD.** McEwen, B.S. *Neuroendocrinology, Rockefeller University, New York, NY.*

Stress represents a response of the body that promotes adaptation and survival in the face of a real or imagined threats to homeostasis. The process is called "allostasis" and it is mainly beneficial. What leads to impaired health and to disease is the overuse or the dysregulation of this response system, and this is referred to as "allostatic load and overload." Allostatic load is seen in animals in the wild as they attempt to maximize reproductive success, whereas allostatic overload is a more extreme version of allostatic load that is more closely associated with disease. The mediators of allostasis include hormones, the autonomic nervous system, neurotransmitters, and the cytokines and chemokines. These systems interact in a nonlinear fashion, operating as a network. Normally, these systems are turned off when the stimulus is over and they are not needed. When they are regulated efficiently, their activity helps to mobilize energy reserves, promote efficient cardiovascular function, enhance memory of important events, and enhance the immune defense toward pathogens. However, if these same mediators remain turned on when not needed or are turned on insufficiently when they are needed, imbalance in the regulatory network results. If this persists, cumulative wear and tear (allostatic overload) result, which can lead to disease. Atherosclerosis, arthritis, diabetes, obesity, depressive illness, and certain types of memory loss are accelerated by allostatic overload. In industrialized societies, these disorders occur with increasing frequency at lower levels of education and income. Complex factors of perception, lifestyle, and stressful life experiences appear to play a role. (McEwen, B.S., *The End of Stress As We Know It*, Elizabeth Norton Lasley Joseph Henry Press, Washington, DC, 2002.)

26. **NUCLEAR RECEPTOR COACTIVATORS IN AN ANDROGEN-RESPONSIVE NEUROMUSCULAR SYSTEM.** O'Bryant, E., and Jordan, C.L. *Neuroscience Program, Michigan State University, East Lansing, MI.*

Although many spinal motoneurons express androgen receptors (ARs), only some grow in direct response to androgens. This paradox suggests that something other than the AR accounts for differences in androgen responsiveness among motoneurons. Steroid receptor cofactors that regulate the transcriptional activity of nuclear hormone receptors such as the AR may underlie such differences in androgen responsiveness. Skeletal muscles also differ greatly in their androgen responsiveness. The levator ani (LA), important for male copulation, depends on adult androgens to maintain its size, whereas the extensor digitorum longus (EDL) does not. Androgens act via ARs in the LA to increase its size, and cofactors likely mediate this response. Using immunohistochemistry, we find that 60% to 80% of motoneurons in lumbar motor pools SNB, DLN, and RDLN robustly express steroid receptor coactivator-1 (SRC-1) and TIF2 (SRC-2), p300, CBP, and cJUN, although cofactor expression does not coincide with differences in androgen responsiveness of these motoneurons. The LA and EDL also show comparable SRC-1 immunoreactivity; nuclei of muscle fibers, fibroblasts, and terminal Schwann cells (TSCs) are SRC-1+. SRC-1 is markedly enriched at neuromuscular junctions (NMJs). In addition to SRC-1+ TSCs (~80%) that cover motor nerve terminals, significantly more myonuclei and fibroblasts at the junction are SRC-1+ (~65%–70%) than outside the junction (~40%). The apparent colocalization of steroid receptor cofactors and androgen receptors in some motoneurons and muscle nuclei is consistent with the idea that cofactors confer direct androgen responsiveness to these cells. Because ARs are also enriched at the NMJ in the LA, SRC-1, and AR may coactivate synapse-specific genes that underlie the androgen-induced growth of SNB motoneuronal dendrites that is also mediated via ARs in the LA. (*Supported by NIH NS-045195.*)

17. **BREEDING THE SUMATRAN RHINOCEROS (*Dicerorhinus sumatrensis*) IN CAPTIVITY: BEHAVIORAL CHALLENGES, HORMONAL SOLUTIONS.** Roth, T.L. *Center for Conservation and Research of Endangered Wildlife, Cincinnati Zoo & Botanical Garden, Cincinnati, OH.*

With fewer than 300 animals surviving worldwide, the Sumatran rhinoceros is considered one of the most endangered mammals on earth. A captive breeding program initiated in the 1980s was to provide a backup population to the declining wild animals. However, at the start of the 21st century, the program had yet to produce a single calf. In nature, these rhinoceroses are solitary and inhabit dense forests, so information about mating behavior and reproductive physiology is scarce. Furthermore, neither male nor female exhibit any reliable behavioral patterns that can be used to detect the female's estrus. Therefore, animals in captivity often were placed together for mating when the female was unreceptive. These introductions typically resulted in aggressive interactions that often led to serious injuries. A study involving serum hormone monitoring and ultrasonography was conducted on a young female rhinoceros over several years. Data collected through this effort eventually unraveled some of the mysteries of Sumatran rhino reproduction. The most surprising finding was that the species is an induced ovulator that exhibits unusual progesterone patterns when not mated. From this study, a scientific method for accurately predicting when the female would be receptive to the male was developed so that animals could be paired safely. Matings resulted in ovulation and pregnancy, but repeated early pregnancy loss posed yet another hurdle to successful reproduction. Finally, during her sixth pregnancy, the female rhinoceros was supplemented with the synthetic progestin, altrenogest. The pregnancy was successfully carried to term, resulting in the first Sumatran rhino calf produced in captivity in 112 years. (*Supported, in part, by the International Rhino Foundation.*)

22. **HIERARCHIES OF STEROID RECEPTOR REGULATION THROUGH COREGULATORS AND SIGNALING PATHWAY CROSSTALK.** Rowan, B., Shah, Y., El-Gharbawy, A., Desouki, M., Kershah, S., Al-Dhaheri, M., and Koterba, K. *Department of Biochemistry, Medical College of Ohio, Toledo, OH 43614.*

Steroid receptor action is dependent on interaction with coactivators and corepressors. SR coactivators (>50 identified) preferentially interact with agonist-bound steroid receptors (SRs) and enhance their transcriptional activity, whereas corepressors interact with either unliganded or antagonist-bound SRs and silence their transcriptional action. Relatively fewer examples of SR corepressors have been identified. In the classical pathway for SR action, the receptor activates gene transcription through direct interaction with DNA at hormone-responsive elements (HRE) and recruitment of coactivators that facilitate receptor stabilization at the promoter. In addition to the classical pathway, SRs also regulate gene transcription through alternate pathways that do not involve direct binding to HRE sequences. These alternate pathways result from binding of the SRs not to DNA, but to other transcription factors at promoters. Because of these direct and indirect paradigms for SR action, coregulator effects on SR target genes must be considered in a gene specific manner. Another level of SR regulation occurs through kinase-dependent phosphorylation of SRs and coregulators. Our work has focused on kinase pathways in promoting the agonist action of the estrogen receptor (ER) antagonist tamoxifen in reproductive tissues. Src kinase promotes the estrogen-like agonist activity of tamoxifen. We detected elevated Src kinase activity in human endometrium, a tissue in which tamoxifen is an agonist. Src kinase activated the coactivator SRC-1, suggesting a potential mechanism for tamoxifen action. Protein kinase A, another kinase that promotes tamoxifen agonist action, indirectly phosphorylates SRC-1 and differentially phosphorylates ERα and ERâ. These studies will identify the tissue-specific fingerprint or ER and coregulator phosphorylation that is required to promote tamoxifen agonist action.