Stressed-Out Genes? How Social Environment Affects Health

February 27, 2011

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The last few years have seen a veritable explosion in gene-environment interaction research. At the cutting edge of this work is a growing understanding of how environmental stress interacts with genes in ways that affect health, the topic of the "Gene-Environment Interplay in Stress and Health" Theme Program, which was chaired by Tim Strauman of Duke University, at the APS 21st Annual Convention. Ahmad R. Hariri of Duke University started off the program, by exploring the neural and genetic underpinning of human anxiety responses to threat. Correlational research has shown a connection between anxiety and increased risk for psychiatric disorders. The question is, how do we lessen anxiety to prevent future disorders? The answer may lie in greater understanding of the neural chemistry and circuitry involved, which may allow us to identify likely points of alteration. Hariri and his team have focused their attention on the amygdala, which, he says, is crucial in translating stressful environmental factors to physiological experience through controlling heart rate, breathing, attention, and the mechanisms for bringing the system back to normal when the threat has passed. To illustrate, Hariri showed a video clip of animals visiting a newscast. While the anchor and animal wrangler are distracted by holding a snake, a lizard jumps from the table onto the anchor, who dramatically cries out and falls to ground while trying to get the lizard off of him. But, just as quickly, he pops back up, says, "Let's get under control here," and it's on with the broadcast.

Clearly the amygdala is powerful, but problems can arise when it's causing too much experiential anxiety and adversely affecting people's lives. Hariri and his colleagues have been investigating the neural chemistry controlling the amygdala. Using a combination of fMRI, PET, and pharmacological alteration of serotonin transporter functioning, they have shown that serotonin is one key molecule in regulating the amygdala. Specifically, the more serotonin there is in the synapse, the greater the response from the amygdala will be, leading to more experiential anxiety. Also, higher levels of serotonin impair communication between the body's feedback loop through which the prefrontal cortex signals the amygdala that it's time to relax.

These research methods have been fruitful, but using them on a large scale is not realistic due to the expense involved and other issues. So, Hariri and his colleagues have turned to genetics. They have identified a specific genetic promoter region associated with a serotonin autoreceptor in which a certain allele combination has less capacity to inhibit the promoter, leading to greater expression of the gene. This leads to more autoreceptors, starting a chain that leads to greater amygdala response, less negative feedback, and, hence, greater anxiety. With more of this kind of work, Hariri and others are identifying the specific genetic markers, chemistry, and neural circuitry that can be modified to help those suffering from anxiety and lower the risk of anxiety-related disorders.

Cornelius Gross and his colleagues at the Mouse Biology Unit of the European Molecular Biology

Laboratory in Monterotondo, Italy are attempting to model a similar genetic pathway in mice. An increasing number of studies (including the oft-cited 2003 *Science* article by Caspi et al.) show that interaction between early environment and genes can contribute to mental illness. Much work has been done in this area to understand how genes can change the way animals respond to stress and resulting changes in the brain. The hope is that new therapeutic approaches could then be developed to directly reverse these changes. As Hariri discussed, different polymorphisms in genes controlling serotonin signaling like the short (S) allele of the 5-HTTLPR in the serotonin transporter gene from the Caspi et al. (2003) study, have been implicated in increased levels of serotonin and, hence, increased brain activity and amygdala-regulated responses to stress. In particular, the 5-HTTLPR S allele has been associated with increased resting brain activity, and increased amygdala response when viewing threatening stimuli and altered coupling between the amygdala and regions of the prefrontal cortex.

To further investigate this allele and how it interacts with the environment to shape behavior, Gross and his team turned to mice, where they can manipulate genes at will using transgenic technology. Because the mouse genome does not include the region of the serotonin transporter gene containing the S allele, the team used heterozygous knockout mice that are missing one of two copies of the gene and, like S allele persons, show a two-fold reduction of expression. To model early life stress, the team used mothers from different strains of mice that provide either high or low levels of maternal care. When placed into a large and unfamiliar square box (open field test), the heterozygous mice exposed to low maternal care showed the least exploration and remained in the corners for long periods, indicating increased anxiety. Further testing showed that this interaction was paralleled by changes in the neural circuitry of the amygdala and hippocampus, two structures showing altered neural activity in humans with the S allele reporting life stress events. In a second study, the team also showed how exposing the heterozygous knockout mice to repeated social defeat also leads to excessive socialÂ avoidance behavior, another hallmark of major depression.Â Curiously, the two environmental stressors — poor maternal care and social defeat in adulthood — induced different changes in neural circuitry in the heterozygous knockout mice, suggesting that these environmental pathogens tap into different adaptive mechanisms in the organism.

Steve Cole of the University of California, Los Angeles, has spent his career investigating the effects of social adversity on the genome, particularly in the immune system. The most basic question Cole has asked is “Does social adversity influence gene expression?” And the answer, he has found, is yes. This is because DNA is really a very small part of the story. The majority of genes are not expressed and those that are need a protein spark to kick into gear, and those proteins are affected by environment. Research by Cole and others has shown that a variety of genes can be affected this way. In his own study of rats, social isolation was associated with an expression change in 9 percent of the rat genome. In humans, social isolation, chronic social stress, family stress and sleep deprivation have all been shown to affect gene expression in immune system pathways like inflammation and antiviral response.

According to Cole, this is how the pathway works: The social environment affects the central nervous system (i.e., increased heart rate or heavier breathing), which induces a change in the peripheral neurobiology of cells (by contributing to the release of compounds like hormones and neurotransmitters). This then leads to the activation or changes in cell signal transduction pathways, which, in turn, affects the production of transcription factors that control gene expression. Cole’s work showing that the progression of the HIV is quicker in socially inhibited people is a striking example of this pathway at work.

Because the environment can change the activity of our genes, this can lead to what Cole refers to as “recursive developmental remodeling.” One environmental occurrence leads to a certain RNA expression and a change in the body. So, the next time this environmental occurrence happens, it is affecting a different body and leading to a different RNA expression and so on. Thus, RNA is our personal history of biologically determined responses to our environment, what Cole calls “intra-organismic evolution.” And although Cole’s talk focused on how experiences can negatively affect us through gene expression, the news wasn’t all bad. Certain variation in genes, like the 5-HTTLPR of the serotonin transporter mentioned earlier, really do seem to be able to moderate negative life events, an exciting avenue of future research in how to use genetics to improve lives.