Gender Differences in Response to Chronic Stress

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The 1950 Nobel Prize for Medicine was awarded to Hench, Kendall and Reichstein for their work leading to the discovery of glucocorticoids, as well as elucidation of their structure and biological effects. A key event leading to the discovery of glucocorticoids and their anti-inflammatory action was the observation that female patients with rheumatoid arthritis often had a dramatic remission when they became pregnant (Hench, 1977). Once the endogenous factor producing this remission, cortisol or hydrocortisone, was identified, studies showed significantly increased plasma glucocorticoids during pregnancy. Upon reflection, the adaptive value of increased glucocorticoids during pregnancy is apparent. Many changes in normal physiology occur in conjunction with the hormonal changes during pregnancy to support development of a healthy fetus. A number of these changes are consistent with known effects of elevated glucocorticoid, including changes in the immune system, cardiovascular function, fluid balance and energy metabolism.

However, chronically elevated glucocorticoids can have profound effects on the normal nervous system function in both positive and negative ways (McEwen, 1998). Some of these effects are reversible over a period of weeks (Luine et al., 1994; Magarinos & McEwen, 1995), but more prolonged exposure may lead eventually to permanent changes (R. Sapolsky et al., 1985). The health related effects of chronic stress are of considerable interest, because a variety of stress-related disorders result in chronic elevation of glucocorticoids, including mild cognitive impairment in aging patients, posttraumatic stress disorder, Cushing's syndrome, and depression (R. M. Sapolsky, 1996). In addition, stress from life events and socioeconomic status or even longterm clinical treatment for chronic inflammatory conditions may have pathological

consequences. How can these deleterious effects of chronically elevated glucocorticoids be reconciled with the exposure of women to elevated glucocorticoids for nine months during pregnancy?

One of the best characterized of these pathological changes in the nervous system is atrophy of neurons in the CA3 region of the hippocampus in male rats and mice (Liu et al., 2006; Watanabe et al., 1992b). The hippocampus plays a role in control of the hypothalamus-pituitary-adrenal gland response to stress and is an important target for glucocorticoids in the nervous system. Hippocampal neurons are important for adaptive behavior as well as certain forms of memory and learning. Structural differences between males and females have been described in the hippocampus. Males have a greater total number of granular neurons in the dentate gyrus and more mossy fiber synapses in the hilus than females, whereas females exhibit a greater number of mossy fiber synapses in the CA3 region (Madeira & Paula-Barbosa, 1993; Madeira et al., 1991). Functional differences between male and female hippocampal function have also been reported, including long-term potentiation and performance of hippocampal-dependent tasks (Roof et al., 1993). However, the physiological and molecular basis for these differences were not well delineated.

Regardless, the chronic elevation of glucocorticoids during pregnancy raised the question of whether males and females also differed in neuronal responses to chronic elevation of corticosterone. Comparisons of neuronal morphologies, neurotransmitter receptor composition and synaptic protein levels in male and female rodent hippocampus exposed to normal and chronically elevated corticosterone indicate that females are remarkably resistant to the effects of chronically elevated glucocorticoids (Galea et al., 1997; Liu, et al., 2006). The ability of the antiepileptic drug phenytoin (Watanabe, et al., 1992a) to block the effects of chronically elevated

glucocorticoids on neuronal activity in hippocampal neurons in males, and certain other observations, implicate excitatory amino acid neurotransmitter receptors in the actions of glucocorticoids (Magarinos & McEwen, 1995). An analysis of glutamate receptor isotypes expressed in male and female mouse hippocampus in response to normal and chronically elevated glucocorticoids have revealed a striking gender-dependent differential shift in the expression of glutamate receptors. Females exhibited increased relative expression of NR2A and GluR2 receptor isotypes compared to males (Liu, et al., 2006). Strikingly, NMDA receptors with NR2A subunits require higher levels of glutamate for activation and exhibit increased sensitivity to inhibition by Zn^{2+} and glycine (Cull-Candy et al., 2001). Similarly, AMPA receptors containing GluR2 subunits are essentially impereant to Ca^{2+} (Swanson, et al, 1997) Kamboj, & Cull-Candy, 1997 (See also Chapter 17). Such changes may reduce the likelihood of excitotoxic damage that is thought to be associated with chronically elevated glucocorticoids (R. Sapolsky, 1990). Understanding the molecular basis for neural damage due to chronic stress may provide new therapeutic strategies to limit such damage. In addition, the recognition of gender specific differences in response to environmental stressors may have important implications for the clinic.

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