Stress reaction is usually activated by the brain, when homeostasis is or perceived to be threatened. The stress signals are transmitted from the brain by two main branches; the sympathoadrenomedullary and the hypothalamo-pituitary-adrenal (HPA) axes and employ neural, humoral and immune pathways to cope with the stressor. Because of its potency, the stress reaction has to be precisely regulated. The HPA axis is regulated by feedback loops where its end product, corticosterone in laboratory rat and mouse, inhibits its activity. The effect of corticosterone does not depend only on the concentration of corticosterone but also on local metabolism of glucocorticoids via oxo-reduction catalyzed by the enzyme 11β -hydroxysteroid dehydrogenase 1 (encoded by the *Hsd11b1* gene), which intracellularly regenerates active corticosterone from inactive 11-dehydrocorticosterone, or by extra-adrenal de novo steroidogenesis of glucocorticoids. We focused on analysis of stress response in experimental animals differing in HPA axis responsivity (Fischer 344 rats (F344) vs. Lewis rats (LEW) and germ-free (GF) vs. specific pathogen free mice (SPF)) with special emphasis on regulation of stress response, glucocorticoid regeneration and influence of gut microbiota. We found that stress modulated local regeneration of glucocorticoids in the limbic structures involved in HPA axis regulation but not in the canonical structures of HPA axis. F344 and LEW rats showed differences in stress-dependent changes of expression of genes involved in HPA axis regulation in limbic areas. Similarly, psychosocial stress upregulated regeneration of corticosterone in lymphoid organs and this effect was more pronounced in LEW than F344 rats. Similarly, inflammatory stress elevated glucocorticoid regeneration in specific microanatomical compartments of the murine gut immune system and expression of *11hsdb1* correlated with the expression of *Tnfα* as well as other cytokines. Microbiota modulated behavior in social conflicts and the response of the HPA axis, colon and mesentery lymph nodes to chronic psychosocial stress. We also demonstrated that microbiota impact the response of the pituitary, adrenals and intestine to acute restraint stress. Together we can conclude that local regeneration of glucocorticoids plays an important role in central feedback regulation of HPA axis response and in local restriction of immune system. The microbiota are involved in modulation not only the HPA response to stress but also behavior and local extra-adrenal glucocorticoid regeneration and de-novo synthesis.