S33-02 - **ROLE OF P-GLYCOPROTEIN FOR THE ACTIONS OF ANTIDEPRESSANTS**

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Clinical studies have demonstrated an impairment of glucocorticoid receptor (GR)-mediated negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis in patients with major depression (GR resistance), and its resolution by antidepressant treatment. This GR impairment is driven by different pathophysiological mechanisms, including the effects of inflammatory mediators, changes in GR-associated proteins, reduction of intracellular access of glucocorticoid hormones, and GR gene variants. Our research has looked at the multitude of pathways affecting GR and MR function, using both clinical models and experimental systems, including most recently the use of prednisolone as a new neuroendocrine test, the in vitro evaluation of GR function in peripheral blood cells from depressed patients, the use of mice with knockout glucocorticoid transporter (p-glycoprotein) genes, and the examination of polymorphisms in inflammatory genes. This presentation will review our most important recent findings in this field, including:

1) that GR in peripheral blood mononuclear cells is resistant to the modulating effects of antidepressants in the context of increased activation and production of interleukin (IL)-6;

2) that p-glycoprotein knockout animals have normal entry of corticosterone into the brain but do not show the effects of antidepressants on the HPA axis;

3) that polymorphisms in the IL-6, IL-10, phospholipase A2 (PLA2) and cyclooxygenase-2 (COX-2) genes regulate the interaction between stress, inflammatory challenges and the development of mood and somatic symptoms; and

4) that, in contrast to the GR, the mineralocorticoid receptor (MR) function remains intact in depression, except in a subgroup of individuals who do not respond to treatment.

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