MODELLING DEPRESSION WITH GLUCOCORTICOID RECEPTOR TRANSGENIC MICE

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Impaired glucocorticoid receptor (GR) signaling is a postulated mechanism for the pathogenesis of major depression. Since *in vivo* expression and functional studies of GR are not feasible in humans, we have generated mouse strains that over- or underexpress GR: i) GR heterozygous mice ($GR^{+/-}$) with a 50% GR gene dose reduction; and ii) GR transgenic mice (YGR) with a 100% gene dose elevation. $GR^{+/-}$ mice exhibit normal baseline behaviors, but demonstrate after stress exposure increased helplessness, a behavioral correlate of depression in mice. Similar to depressed patients, $GR^{+/-}$ mice have a disinhibited HPA system and a pathological DEX/CRH test. Thus, they represent a murine depression model with good face and construct validity. YGR mice, in contrast, show reduced helplessness after stress exposure, and an improved HPA system feedback regulation. Therefore they are a model for a stress-resistant strain. These models can be used to study plasticity changes underlying the pathogenesis of depressive disorders. As first potential molecular correlate we identified a downregulation of BDNF in the hippocampus of $GR^{+/-}$ mice. Translational approaches, i.e. how to use these models specifically for clinically relevant questions, will be discussed.