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Glucocorticoid-induced, rapid serotonin release by serotonergic neurons *in vitro*

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Disturbances in the serotonergic neurotransmitter system and the body's stress response play a pivotal role in the pathogenesis of many psychiatric diseases, particularly in depression. As mediators of the hypothalamic-pituitary-adrenal axis, glucocorticoids affect serotonergic neurons and vice versa. Previous research suggested that glucocorticoids rapidly increase extracellular hippocampal serotonin, but the cellular mechanisms of glucocorticoid-induced serotonin release are unknown. Murine stem cell-derived serotonergic neurons (1C11-5HT) and vesicular dyes FFN511 and FM4-64FX were employed to visualize rapid, somatodendritic vesicular 5-HT release upon glucocorticoid receptor activation. Extracellular calcium was dispensable for rapid vesicular release. After subcellular fractionation of mice central nervous systems, glucocorticoid receptor and the synaptic markers rab3 and synapsin 1 were immunologically detected in the membrane/vesicular fractions. In immunofluorescence of 1C11-5HT, glucocorticoid receptor and the vesicular marker synaptotagmin 1 showed strong colocalization, which is a prerequisite for an interaction of glucocorticoid receptor with vesicular release sites to trigger 5-HT release. Further, colocalization of glucocorticoid receptor and the membrane-bound serotonin transporter was determined after glucocorticoid receptor activation. 15 min after its activation, spatial proximity between glucocorticoid receptor and the membrane-bound serotonin transporter increased, which is a prerequisite for a possible interaction. 30 min after its activation, however, colocalization dropped below initial levels. This work extends the understanding of the interplay between glucocorticoids and serotonergic neurons. In turn, this might ultimately help understand the underlying mechanisms in the pathogenesis of psychiatric diseases such as depression.