Relating cerebral serotonin 2A receptor and serotonin transporter binding to personality and familial risk for mood disorder

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ABSTRACT

This dissertation focuses on pre- and postsynaptic characteristics of serotonergic neurotransmission in the living human brain and their relation to personality and familial risk factors for mood disorders. The studies were conducted at Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet.

Mood disorders are common with a life time risk of major depression of at least 10% being twice as common in females as in males. The most potent risk factor for developing a mood disorder is a family history of mood disorder, but the specific factors mediating the effects are not well understood. Disadvantageous combinations of genetic profile, environmental stress factors, and disturbances in serotonergic neurotransmission seem to be important in the pathophysiology. Concerning the disturbances in serotonergic neurotransmission, it is not clear whether they represent trait or state markers of mood disorders.

The thesis is based on three studies that aim at exploring possible trait characteristics of mood disorders by linking personality and familial risk factors and brain biology in terms of serotonin 2A receptor and serotonin transporter binding and distribution. Serotonin 2A receptor and serotonin transporter binding was measured by in vivo neuroimaging (positron emission tomography). In study 1 we examined the possible association between the personality risk factor, neuroticism, and serotonin 2A receptor binding in regions of relevance to personality and mood disorders in a large sample of healthy volunteers. We identified a link between high neuroticism and high frontolimbic serotonin 2A receptor binding. Based on these findings, we hypothesized that this link might be mediated by genetic risk factors for mood disorders. Further, we hypothesized that the serotonin transporter binding in brain regions relevant to mood disorders might also represent a trait characteristic of mood disorder. These hypotheses were explored in a high-risk low-risk study design comparing twins at high familial risk with twins at very low risk of developing mood disorders. We found a more pronounced coupling between neuroticism and frontolimbic serotonin 2A receptor binding in individuals at high than at low familial risk of mood disorder (study 2). Also, we found a lower SERT binding in dorsolateral prefrontal cortex and anterior cingulate in individuals at high familial risk (study 3).

In conclusion, the results generated from this work suggest that alterations in the serotonergic neurotransmission may represent a trait marker of mood disorders that could either be established during early brain development and/or compensatory adaptations to low synaptic serotonin. Thus our findings offer a neurobiological link between personality and familial risk factors and mood disorders. This may guide future longitudinal studies aiming at elucidating which characteristics of serotonergic neurotransmission are typical for at-risk individuals who develop mood disorder.