

On the importance of inflammation for personality traits and psychiatric morbidity

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Avhandlingen baseras på följande delarbeten:

- I. **Petra Suchankova**, Susanne Henningsson, Fariba Baghaei, Roland Rosmond, Göran Holm, Agneta Ekman. Genetic variability within the innate immune system influences personality traits in women. *Genes Brain and Behavior* 2009. **8**:212-7
- II. **Petra Suchankova**, Göran Holm, Lil Träskman-Bendz, Lena Brundin, Agneta Ekman. The +1444C>T polymorphism in the *CRP* gene is associated with impulsiveness and suicidal behaviour. *Submitted Manuscript*
- III. **Petra Suchankova**, Fariba Baghaei, Roland Rosmond, Göran Holm, Henrik Anckarsäter, Agneta Ekman. Genetic variability within the *S100B* gene influences the personality trait self-directedness. *Psychoneuroendocrinology* 2010. *In press*
- IV. **Petra Suchankova**, Jonas Klang, Carin Cavanna, Göran Holm, Staffan Nilsson, Erik Jönsson, Agneta Ekman. Is the Gly82Ser polymorphism in the RAGE gene of relevance for schizophrenia and the personality trait psychoticism? *Submitted Manuscript*
- V. **Petra Suchankova**, Staffan Nilsson, Aleksander Mathé, Agneta Ekman. Expression of S100B in a genetic rat model of depression – a pilot study. *Preliminary Manuscript*

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ABSTRACT

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Background: Pro-inflammatory mediators have been implicated in processes that could be both beneficial and toxic to cells in the brain. On the one hand balanced levels of these mediators favour e.g. neurodevelopmental processes, while on the other hand disturbances in this delicate balance, facilitated by activation of microglia and astrocytes for instance, may result in detrimental effects via interference with e.g. neural plasticity. Accumulating reports are linking raised serum levels of pro-inflammatory mediators to patients suffering from psychiatric morbidity and the underlying mechanisms need to be studied. This thesis focuses on four different inflammation-related proteins suggested to be associated with brain function. Firstly, C-reactive protein (CRP) - an acute phase reactant previously correlated with certain personality traits and depression as well as cardiovascular diseases. Secondly, complement factor H (CFH) - an important regulator of the complement cascade that has been implicated in e.g. Alzheimer's disease. Thirdly, the astrocyte-derived protein S100B - the levels of which has been found to be raised in serum of suicide attempters, and of depressed and schizophrenic patients. Fourthly, the receptor for advanced glycation end products (RAGE) - suggested to induce the pro-inflammatory effects of S100B in the brain and implicated in schizophrenia. The aim of this thesis was to i) investigate the possible influence of polymorphisms located in these genes on personality traits in population-based cohorts as well as in suicide attempters, ii) assess whether polymorphisms in *CRP* and *RAGE* increase susceptibility to suicidal behaviour and schizophrenia, respectively, and iii) investigate the level of gene expression of S100B in different brain regions in a genetic rat model of depression (Flinders sensitive line) and examine whether this expression is altered by immune activation. **Results:** The studied polymorphisms were associated with various personality traits in the normal population. The polymorphism +1444C>T located in the *CRP* gene was associated with increased scores of impulsivity both in a population-based cohort and in suicide attempters. The same allele was also found to increase the risk of suicidal behaviour. A polymorphism (Gly82Ser) in *RAGE* was associated with increased scores of the personality trait psychoticism in the normal population and was further associated with increased susceptibility of schizophrenia in patients. In addition, baseline mRNA levels of S100B were up-regulated in several brain regions in the spontaneously depressed rat when compared to control animals. **Conclusions:** The work presented in this thesis supports the hypothesis that inflammatory processes may be of importance for both normal behaviour and psychiatric morbidity. Due to the established connection between low-grade inflammation, cardiovascular diseases and psychiatric disorders, our results may further reflect the possibility that these disorders share a common genetic background.

Key words: inflammation, C-reactive protein, complement factor H, S100B, receptor for advanced end products, polymorphisms, gene expression, personality traits, suicidal behaviour, schizophrenia, depression, Flinders sensitive line

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