Brain Behav Immun. 2015 Sep 20. pii: S0889-1591(15)30020-9. doi: 10.1016/j.bbi.2015.09.013. [Epub ahead of print]

# Antibodies to ß adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome.

Loebel M[1], Grabowski P[2], Heidecke H[3], Bauer S[2], Hanitsch LG[2], Wittke K[2], Meisel C[4], Reinke P[5], Volk HD[6], Fluge Ø[7], Mella O[8], Scheibenbogen C[6].

**Abstract**

Infection-triggered disease onset, chronic immune activation and autonomic dysregulation in CFS point to an autoimmune disease directed against neurotransmitter receptors. Autoantibodies against G-protein coupled receptors were shown to play a pathogenic role in several autoimmune diseases. Here, serum samples from a patient cohort from Berlin (n= 268) and from Bergen with pre- and post-treatment samples from 25 patients treated within the KTS-2 rituximab trial were analysed for IgG against human α and ß adrenergic, muscarinic (M) 1-5 acetylcholine, dopamine, serotonin, angiotensin, and endothelin receptors by ELISA and compared to a healthy control cohort (n=108). Antibodies against ß2, M3 and M4 receptors were significantly elevated in CFS patients compared to controls. In contrast, levels of antibodies against α adrenergic, dopamine, serotonin, angiotensin, and endothelin receptors were not different between patients and controls. A high correlation was found between levels of autoantibodies and elevated $IgG_{1-3}$ subclasses, but not with $IgG_4$. Further patients with high ß2 antibodies had significantly more frequently activated HLA-DR+ T cells and more frequently thyreoperoxidase and anti-nuclear antibodies. In patients receiving rituximab maintenance treatment achieving prolonged B-cell depletion, elevated ß2 and M4 receptor autoantibodies significantly declined in clinical responder, but not in non-responder. We provide evidence that 29.5% of patients with CFS had elevated antibodies against one or more M acetylcholine and ß adrenergic receptors which are potential biomarkers for response to B-cell depleting therapy. The association of autoantibodies with immune markers suggests that they activate B and T cells expressing ß adrenergic and M acetylcholine receptors. Dysregulation of acetylcholine and adrenergic signalling could also explain various clinical symptoms of CFS.