The partial genetic deletion of DAT causes a sex-specific imbalance in Th17/Treg cells: a role for adrenomedullin?

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Genetic factors are strongly involved in mental disorders. Several studies have found a correlation between altered dopamine transmission and such psychiatric diseases as attention deficit hyperactivity disorder (ADHD) and schizophrenia (1). In particular, mice lacking the dopamine transporter (DAT) are characterized by high extracellular dopamine levels and spontaneous hyperlocomotion (2) and have been suggested as a relevant model of ADHD. Several studies (3,4) have also shown that male patients with psychiatric diseases show high peripheral levels of Adrenomedullin (ADM)(5), a regulatory peptide known to influence cerebral activity (6). We have demonstrated that ADM and its receptor protein RAMP2 are expressed in thymus (7), where they probably play a role in T cell maturation. It is known that an association exists between autoimmune and psychiatric diseases: in schizophrenic patients the prevalence of autoimmune disorders is 53% (8). It has been observed that ADM administration modulates Th17 and Treg peripheral levels in mouse models of rheumatoid arthritis and multiple sclerosis (9,10). In this project we focused on the possible effect of thymic ADM in the maturation of Th17 and Treg in a validated model of ADHD (DAT +/- mice), by examining the activation of the canonical NF-kB pathway (p50 and p65 subunits), a transcription factor involved in T cell maturation, which is activated in many autoimmune diseases. To this purpose, ADM, RAMP2, RORγt (a marker of Th17 cells) and IL-10 (a marker of Treg cells) gene expressions in thymic tissue of control and DAT +/- mice were measured by means of real time PCR. The activation of NF-kB was evaluated by measuring the expression of its p50 and p65 subunits in nuclear thymic fractions by means of Western blot analysis. Gene expressions of ADM and its receptor protein RAMP2 significantly increased in thymi of DAT+/- male mice with respect to male controls ($p<0.01$, and $p<0.001$, respectively), whereas the expression of these genes was drastically downregulated in thymi of DAT+/- female mice ($p<0.001$ with respect to female controls). As regards NF-kB, p65 nuclear expression was significantly lower in DAT+/- female mice ($p<0.05$), and remained virtually unchanged in DAT+/- male mice. At variance with p65, p50 nuclear expression increased significantly in DAT+/- male mice ($p<0.001$), whereas it decreased, although to a non significant extent, in DAT+/- female mice. Consistent with these observations, a significant increase in RORγt gene expression was found in DAT +/- male mice ($p<0.01$), whereas IL-10 gene expression was found to be dramatically decreased ($p<0.001$). In DAT+/- female mice, no significant changes were observed either in RORγt or in IL10 gene expression with respect to female controls.
It has been observed that males are considerably more likely to be diagnosed with ADHD than females; the course of the disorder and its associated co-morbidities also appear to be sensitive to sex (11). In this study, we demonstrated a sex-specific increase of ADM in a validated animal model of ADHD, and consistently observed an increase in the Th17 to Treg ratio, which is known to play a role in the etiopathogenesis of several autoimmune diseases. Therefore, the possibility that an immune system dysfunction can concur in the pathogenesis of mental disorders such as ADHD deserves further investigation.

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