Gender related differences in expression of dopaminergic receptors on human circulating CD4+ T cell subsets

N. Kustrimovic, E. Rasini, M. Legnaro, B. Dongmo, F. Marino, M. Cosentino

Center of Research in Medical Pharmacology, University of Insubria, Varese, Italy

Dopamine (DA) is one of the most important neurotransmitters in the central nervous system, and exerts its actions through dopamine receptors (DR) that are classified into D1-like and D2-like subclasses on the basis of pharmacological and biochemical differences. Nowadays five different DR have been identified (the D1-like DRD1 and DRD5, and the D2-like DRD2, DRD3 and DRD4).

Recent evidence indicates that DA exerts direct effects on immune cells which may have clinical and therapeutic relevance in several fields, including autoimmune disease, cancer, and neuroinflammation (*Cosentino and Marino, 2013; Buttarelli et al., 2011; Cosentino et al., 2007*), however little work has been done to examine their expression and functional relevance in immune system cells.

In the present study we examined the expression of DR on circulating CD4+ T lymphocytes of normal healthy individuals, namely 16 female donors (age [mean ± SD]: 58.0±13.5 years) and 7 male donors (age: 59.7±13.9 years). Lymphocytes were separated from whole blood by Ficoll-hypaque density gradient centrifugation and flow cytometry was used to determine the pattern of expression of D1-like and D2-like DR on different CD4+ T-cell subsets, specifically naive (CD3+CD4+CD45RA+CCR7+), T central memory (Tcm, CD3+CD4+CD45RA-CCR7+) and T effector memory (Tem, CD3+CD4+CD45RA-CCR7-) subsets.

Results showed no significant difference in the percentages of CD3+ lymphocytes between male and female subjects (mean±SEM: 69.3±3.9% vs 73.5±2.2%) however male subjects had significantly lower percentage of CD4+ T cells compared to female donors (45.8±2.3% vs 51.9± 2.1%, $P<0.05$).

No differences between male and female donors was found as regards distribution of CD4+ T cells into Tcm (36.4±4.6% vs 28.5±2.3%), Tem (27.0±4.2% vs 23.0±1.9%) and naive T cells (36.1±8.7% vs 43.9±3.2%).

All five DR were expressed on CD4+ T cells. In both male and female subjects expression of D1R-like DR was significantly higher than that of D2-like DR. Results revealed several gender-related differences in the expression of DR on CD4+ T cell subsets. Namely, expression of DRD1 and DRD5 was significantly higher in male subjects (DRD1 13.6±1.9% vs 7.5±1.5%, $P<0.01$, and DRD5 16.1±1.1% vs 11.4±2.1%, $P<0.05$), and also expression of DRD3 was higher in CD4+ T cells of male subjects (11.0±2.3% vs 4.7±0.8%, $P<0.01$). Even though expression of DRD2 and DRD4 was higher in male subjects differences so far did not reach the statistical significance (DRD2 4.7±1.6% vs 2.2±0.4%, and DRD4 12.3±2.3% vs 7.9±2.2%).

In male donors, expression of DRD1, DRD2 and DRD4 was highest in Tem cells, while expression of DRD5 was highest in naive T cells. In female subjects, on the contrary, expression of DRD5 was highest in Tem, while expression of all the other DR was similar in all CD4+ T cell subsets.

In conclusion, the present study has shown that human CD4+ T lymphocytes express both D1-like and D2-like DR, although to a different extent, and that significant differences occur between female and male subjects. Further studies are needed to establish the functional role of such receptors. In particular, also in view of the role of DA and DR in the modulation of the immune response, studies are warranted to assess the possible relationship between gender-related differences in DR expression on human lymphocytes and the different susceptibility of females and males to immune-related disease (*Whitacre, 2001; Ahmed et al., 1985*). Clarifying the role of DR on immune cells will allow exploiting the immunomodulatory potential of several dopaminergic agents, already in clinical use for non-immune indications and with a usually favourable risk-benefit profile.

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