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Dopamine up-regulates Th17 phenotype from individuals with generalized anxiety disorder☆,☆☆

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ABSTRACT

Our objective was to evaluate the effect of stress-related dose of dopamine (DA) on the *in vitro* proliferation and cytokine production in polyclonally-activated T cells from healthy individuals or individuals with generalized anxiety disorder (GAD). Our results demonstrated that cell cultures from GAD group proliferated less following T cell activation, as compared with control group. The addition of DA reduced the proliferative response in cell cultures from healthy but not from GAD individuals. The cytokine profile in GAD individuals revealed Th1 and Th2 deficiencies associated with a dominant Th17 phenotype, which was enhanced by DA. A similar DA-induced immunomodulation was also observed in PPD-activated cell cultures from GAD individuals. Unlike the control, DA-enhanced Th17 cytokine production in GAD individuals was not affected by glucocorticoid. In conclusion, our results show that the T cell functional dysregulation in GAD individuals is significantly amplified by DA. These immune abnormalities can have impact in increasing the susceptibility of individuals with anxiety disorders to infectious diseases and inflammatory/autoimmune disorders.

1. Introduction

It is now known that the immune system is regulated by central as well as peripheral sympathetic nervous system. This is primarily achieved by cathecolamines, such as dopamine (DA), which interact with different effector immune cells and thereby ultimately regulate the homeostatic response of an individual to environmental stresses (Sarkar et al., 2010).

In the central nervous system, DA plays an essential role as neurotransmitter by playing diverse functions including movement (Cenci, 2007), drug addiction (Dayan, 2009), pain perception (Potvin et al., 2009), hormone secretion (Ben-Jonathan and Hnasko, 2001), motivation and pleasure (Wise, 2008). At the peripheral level, sympathetic innervations of organs and tissues, such as lymph nodes and spleen, can be controlled by dopaminergic signaling, particularly during stress (Bencsics et al., 1997).

DA exerts its effects in susceptible cells by stimulating DA receptors (DARs) expressed on the cell surface of neurons. Five DARs have been described so far (D1–D5); DARs are hepta-spanning membrane receptors and belong to the superfamily of the G protein-coupled receptors (Strange, 1993). Whereas type I DARs (D1 and D5) are generally coupled to Gαs and stimulate cAMP production, type II DARs (D2, D3 and D4) are often coupled to Gαi promoting inhibition of cAMP synthesis (Sibley et al., 1993). This differential coupling of DARs allows DA to promote distinct effects in the same cell expressing the two different kinds of DARs.

Besides its conventional role as neurotransmitter, DA is now considered to play a pivotal role in neuroimmune communications. The first clue to this possibility was the observation that DARs are expressed in normal human leukocytes (McKenna et al., 2002; Ferrari et al., 2004; Kirillova et al., 2008; Nakano et al., 2008, 2009). Interestingly, in schizophrenic patients, who have a hiperdopaminergic activity (Birtwistle and Baldwin, 1998), severe abnormalities of immune functions have been demonstrated, such as alterations in T-cell subsets, production of cytokines, and effector functions (Muller et al., 2000; Strous and Shoenfeld, 2006; Riedel et al., 2007). Furthermore, it is known that psychological stress causes an increase in peripheral release of DA (Sinha, 2008), and individuals suffering from chronic stress, like those with generalized anxiety disorder (GAD), are more susceptible to infectious diseases by damaging Th1-mediated immune response (Boscarino, 2004; Koh and Lee, 2004; Sareen et al., 2005; Schneiderman

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