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The immunoregulatory role of dopamine: an update

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Abstract

The neurotransmitter dopamine (DA) is an important molecule bridging the nervous and immune systems. DA through autocrine/paracrine manner modulates the functions of immune effector cells by acting through its receptors present in these cells. DA also has unique and opposite effects on T cell functions. Although DA activates naïve or resting T cells, but it inhibits activated T cells. In addition, changes in the expression of DA receptors and their signaling pathways especially in T cells are associated with altered immune functions in disorders like schizophrenia and Parkinson's disease. These results suggest an immunoregulatory role of DA. Therefore targeting DA receptors and their signaling pathways in these cells by using DA receptor agonists and antagonists may be useful for the treatment of diseases where DA induced altered immunity play a pathogenic role.

Keywords

dopamine; immunity; T cells; dendritic cells; macrophages; NK cells; B cells; microglia

1. Introduction

Besides conventional roles of neurotransmitters in neural communication, a large amount of evidence indicates that neurotransmitters mediate cross talk between the nervous and immune systems (Eskandari and Sternberg, 2002). Among these neurotransmitters, the role of DA is particularly interesting because in addition to regulating behavior, movement, endocrine, cardiovascular, renal and gastrointestinal functions (Basu et al., 1995; Chakroborty et al., 2008; Mezey et al., 1999; Missale et al., 1998), DA can also modulate immune functions (Basu and Dasgupta, 2000). DA is synthesized by different immune effector cells and its receptors are present in these cells (Basu et al., 1993; Basu and Dasgupta, 2000; Eldrup et al., 1989; Ferrari et al., 2004; Kirillova et al., 2008; Le Fur et al., 1980; McKenna et al., 2002; Nakano et al., 2008, 2009). Furthermore the sympathetic

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innervation of lymphoid tissues can also be dopaminergic in nature, particularly during stress (Bencsics et al., 1997; Mignini et al., 2003). As the majority of recent reports indicate unique interactions between dopamine and T cells, the main focus of this mini-review is on DA mediated regulation of T cell function.

2. DA modulate the functions of immune effector cells by acting through its receptors present in these cells

DA is a monoamine catecholamine neurotransmitter, which acts through its D_1 and D_2 classes of receptors present in the target cells (Missale et al., 1998). The D_1 class includes the D_1 and D_5 subtypes, which on activation increase intracellular cAMP (Missale et al., 1998). In contrast, the D_2 class of receptors, which includes D_2, D_3, and D_4 subtypes, inhibits intracellular cAMP on stimulation (Missale et al., 1998).

Several studies now indicate the presence of DA D_1 D_2, D_3, D_4 and D_5 receptors in normal human leukocytes (Ferrari et al., 2004; Kirillova et al., 2008; McKenna et al., 2002; Nakano et al., 2008, 2009). Among the leukocyte subpopulations, T lymphocytes, monocytes have low, neutrophils, eosinophils have moderate and B, NK cells have high and more consistent expression of DA receptors (McKenna et al., 2002). In addition, DA D_1 receptors are present in human dendritic cells (Nakano et al., 2008). Recently DA uptake system has been identified in the lymphocytes (Amenta et al., 2001; Caronti et al., 2001; Mill et al., 2002).

Furthermore, dopaminergic innervation of lymphoid tissues through sympathetic nerves has also been described, thereby suggesting direct DA-mediated neural regulation of immune effector cells (Bencsics et al., 1997; Mignini et al., 2003). Although these cells primarily come in contact with DA in lymph nodes, spleen, bone marrow and circulation (Basu and Dasgupta, 2000), but DA synthesized and released by T and dendritic cells can also act on DA receptors present in the T cells through an autocrine/paracrine loop (Bergquist, et al., 1994; Cosentino, et al., 2007; Nakano et al., 2009). DA regulates several important functions of these cells (Besser et al., 2005; Ghosh et al., 2003; Levite et al., 2001; Saha et al., 2001a, 2001b; Sarkar et al., 2006; Watanabe et al., 2006). Thus understanding the changes in the immune disorders associated with abnormal dopaminergic activities will help to elucidate the immunomodulatory role of this important neurotransmitter (Basu and Dasgupta, 2000).

3. Altered immunity is seen in diseases with abnormal dopamine function

Altered immune functions have been observed in diseases like schizophrenia and Parkinson's disease with abnormal dopaminergic systems (Ilani et al., 2001; Nagai et al., 1996; Wandinger et al., 1999). A significantly higher expression of DA D_3 receptors and increased IFN-γ synthesis by T cells are reported in untreated schizophrenic patients (Boneberg et al., 2006; Ilani et al., 2001). On the contrary, decreased expression of DA D_3 receptors and IFNγ synthesis by peripheral lymphocytes are seen in Parkinson's disease (Nagai et al., 1996; Wandinger et al., 1999). Because DA D_3 receptor mediated increase in IFNγ synthesis by T cells has been demonstrated (Ilani et al., 2004), therefore these immune abnormalities are probably due to the changes in expression of DA D_3 receptors and its signaling pathways in the T cells of patients with schizophrenia and Parkinson's disease (Ilani et al., 2004).

Furthermore as dysfunction of the central dopaminergic system is associated with Parkinson's disease and schizophrenia, it will be therefore important to mention here that animal studies have indicated brain DA mediated regulation of peripheral immune functions (Basu and Dasgupta, 2000). It has also been recently shown that central dopaminergic

hypoactivity increases the risk of inflammation during infection or tissue injury (Engler et al. 2009).

4. DA regulates the functions of immune effector cells through autocrine/paracrine loop

CD4+CD25+ regulatory T lymphocytes (Tregs) are specialized T cells, which play a key role in the control of immune homeostasis (Cosentino et al., 2007). Recently, it has been demonstrated that Tregs contain substantial amounts of dopamine (Cosentino et al., 2007), which after being released acts on the DA D_1 receptors present in these cells and subsequently suppress IL-10 and TGFβ synthesis by these cells (Cosentino et al., 2007). In addition, the released DA by acting on DA D_1 receptors down-regulates Treg-dependent inhibition of effector T-lymphocyte proliferation and this occurs without affecting the production of TNFα or IFNγ (Cosentino et al., 2007).

Similarly, a paracrine regulatory loop of DA has been shown in the interface of dendritic and T cells (Nakano et al., 2009). DA stored in human monocytic-dendritic cells following its release acts on the D_1 receptors present in the naïve T cells, increase cyclic AMP and cause differentiation of these cells into T_h2 lineage in response to anti-CD3 plus anti-CD28 mAb (Nakano et al., 2009). However, in absence of dopamine release, T cell differentiation shifts towards T_h1 lineage (Nakano et al., 2009). DA is released from these cells following antigen-specific dendritic-T cell interaction (Nakano et al., 2009). Furthermore as stimulation of cAMP increase DA concentration in dendritic cells and because DA by acting through its D_1 receptors can increase cAMP concentration, therefore it is possible that the released DA auto-regulates its synthesis in these cells via acting through DA D_1 receptors present in these cells (Nakano et al., 2009). These findings indicate that endogenous DA subserves an autocrine/paracrine regulatory loop in the cells of the immune system (Cosentino et al., 2007; Nakano et al., 2009).

5. DA activates resting T cells in absence of any additional stimulating agent

Stimulation of DA D_2 and D_3 receptors in normal resting peripheral human T lymphocytes, activate α4β1 and α5β1 integrins in these cells, thereby promoting adhesion of these cells to the extracellular matrix component, fibronection (Levite et al., 2001). This action of DA may be critical for trafficking and extravasation of T cells across the blood vessels and tissue barriers (Levite et al., 2001). This study is supported by Watanabe et al., 2006 who have shown that DA stimulates adhesion of $CD8^+$ T cells to fibronectin and ICAM through integrins. These authors have further demonstrated that DA induced chemotactic migration of naïve $CD8^+$Tcells is synergistic with chemokines like CCL19, CCL21 and CXCL12 (Watanabe et al., 2006). This action of DA is reported to be mediated through its D_3 receptors present in these cells (Watanabe et al., 2006). DA is also reported to induce cytokine secretion by resting T cells (Besser et al., 2005). It has been shown that stimulation of DA D_3 and D_1/D_5 receptors increase the secretion of TNFα and stimulation of DA D_2 receptors induce IL-10 secretion without affecting the secretion of IFNγ and IL-4 (Besser et al., 2005) (Fig. 1A).

6. DA inhibits activation of stimulated T cells

Although DA activated resting T cells, but anti CD3 and IL-2 induced proliferation and cytotoxicity of $CD4^+$ and $CD8^+$ T cells collected from normal human subjects are significantly inhibited when these cells are treated *in vitro* with high DA concentration observed in the plasma (48.6 pg/ml) of lung cancer patients suffering from uncoping stress

(Saha et al., 2001a, 2001b). The molecular mechanism of this action is attributed to DA D_1 receptor induced increase in the intracellular cAMP (Saha et al., 2001a, 2001b). Similarly, stimulation of DA D_2 and D_3 receptors in T cells has been shown to inhibit activated T cell receptor induced cell proliferation, and secretion of IL-2, IFNγ and IL-4 by down regulating the expressions of non receptor tyrosine kinase lck and fyn (Ghosh et al., 2003) (Fig. 1B).

We have also recently shown that stimulation of DA D_4 receptors in human T cells during T cell receptor activation is associated with its quiescence (Sarkar et al., 2006). DA induces quiescence of these cells by upregulating the transcription factor, KLF2 via inhibition of ERK1/ERK2 in these cells (Sarkar et al., 2006) (Fig. 1B).

7. DA modulates the functions of NK cells, Splenic cells, Macrophages, B cells and Microglial cells

There are reports which indicate that DA can also modulate the functions of other cells in the immune system (Basu and Dasgupta, 2000). Although Reduced NK cell activities and ovalbumine induced delayed type hypersensitivity responses are reported in animals with hyperdopaminergic systems (Teunis et al., 2004; Kavelaars et al., 2005), but increased LPS-induced cytokine production by macrophages and ovalbumine induced humoral responses have been observed in these animals (Kavelaars et al., 2005).

Moreover, DA treatment has shown to stimulate the proliferation of murine splenocytes by acting through its D_2 receptors present in these cells (Carr et al., 2003). A recent report indicates DA mediated inhibition of proliferation in both resting and malignant B lymphocytes (Meredith et al., 2006). Also, DA promotes apoptosis in cycling B cells through oxidative stress. However this action of DA is not demonstrated in resting lymphocytes (Meredith et al., 2006).

Microglial cells are the important immune effector cells in the brain (Chang and Liu, 2000; Färber et al., 2005; Orr et al., 2005; Theodore et al., 2008). After CNS infection, exposure to inflammatory stimuli, or interaction with blood-derived cells, these cells become activated to perform several innate immune functions, including induction of inflammation, cytotoxicity, and regulation of T-cell responses through presentation of antigen. Recent studies have demonstrated the presence of both DA D_1 and D_2 classes of receptors in the microglial cells (Chang and Liu, 2000; Färber et al., 2005). DA by acting via its D_1 receptors regulates the synthesis of microglial nitric oxide, an immune mediator with high antiviral activity (Chang and Liu, 2000; Färber et al., 2005). It has been also shown that DA regulates the migration of these cells *in vitro* by acting through its receptors present in these cells (Färber et al., 2005).

8. Summary and conclusions

Taken together, the studies outlined above indicate that there is a well defined dopaminergic system in immunity (Basu and Dasgupta, 2000), DA is an important regulator of normal immunity (Basu and Dasgupta, 2000) and changes in the status of DA concentrations and/or receptors, especially in the T cells are responsible for abnormal immune functions seen in patients with schizophrenia and Parkinson's disease (Ilani et al., 2001, 2004; Nagai et al., 1996; Wandinger et al., 1999). It will be therefore interesting to study if this DA mediated changes in the immune system is also linked to the etiology of these diseases (Ilani et al., 2001, 2004; Nagai et al., 1996; Wandinger et al., 1999).

Because a recent report indicates functional dopaminergic system in the thymus of rats (Mignini et al., 2009), therefore DA may have a role in the maturation and selection of

lymphocytes (Mignini et al., 2009). It will therefore be prudent to investigate whether DA has any role in the formation of memory T cells since DA is not only synthesized in T cells, but there is also a functional dopaminergic autocrine regulatory loop in these cells (Bergquist, et al., 1994; Cosentino, et al., 2007). Therefore, elucidation of the detailed mechanisms by which DA activates resting T cells and inhibits stimulated T cells will be necessary to design new and effective therapies in future to modulate the functions of T cells in both health and diseases.

Finally, and most importantly, DA and its agonists or antagonists are being used in the clinics at present for the treatment of other diseases (Katzung, 2004); therefore rapid clinical trials may be undertaken using these inexpensive drugs for the treatment of immune disorders. However these drugs should be used with caution in patients with microbial sepsis as it may suppress the immune functions in these patients (Oberbeck, et al., 2006).

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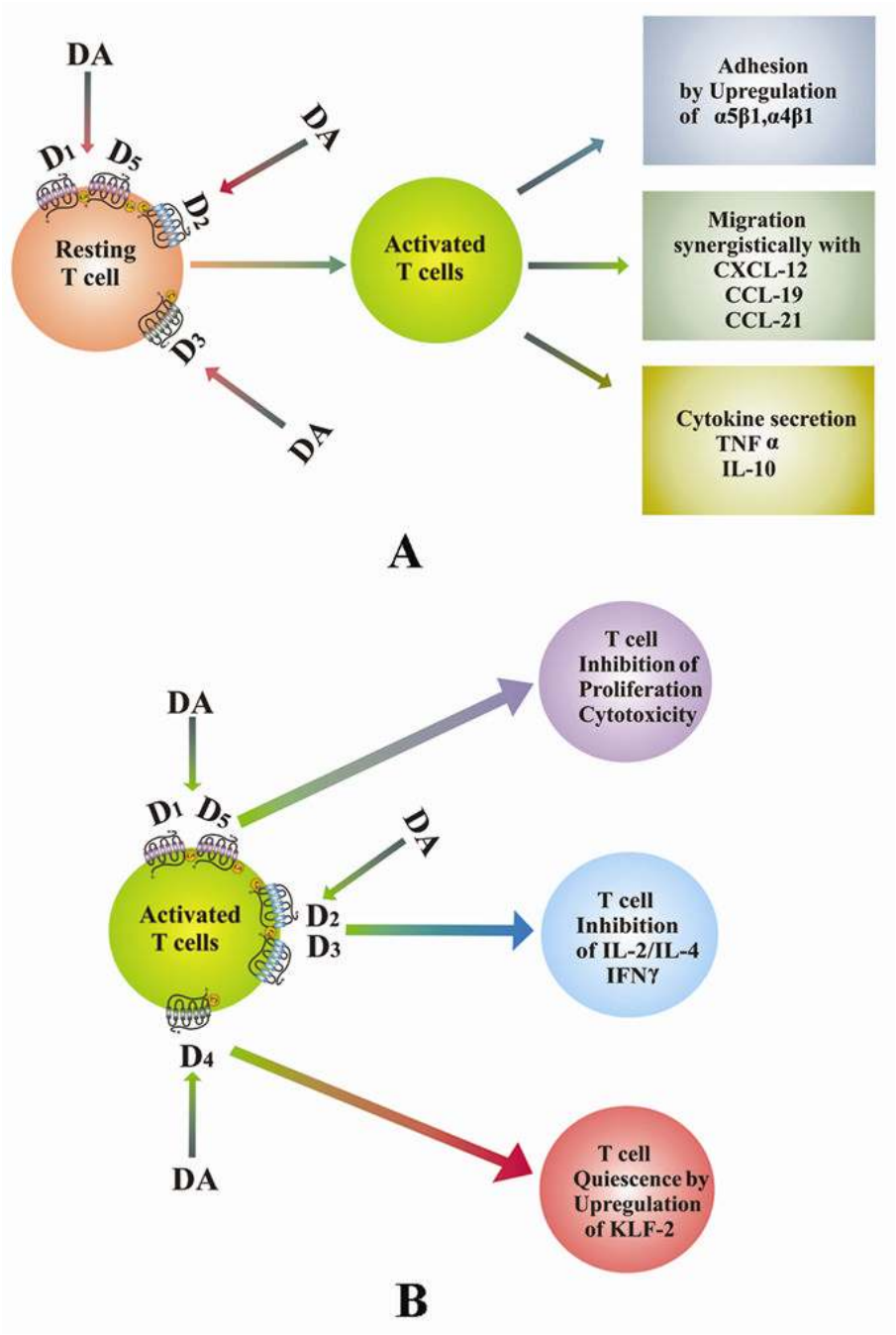

Fig. 1.

Role of dopamine in T cell functions. (**A**). DA activates naïve or resting T cells. DA by acting through its receptors stimulates adhesion, migration and cytokine secretion by these cells. (**B**). DA inhibits activated T cells. DA inhibits the activation of T cells when present during stimulation of T cell receptors and thus inhibits proliferation, cytokine secretion and induces T cell quiescence in these cells by acting through DA receptors. DA, dopamine; D1–D5, dopamine D1–D5 receptors.