NEUROTRANSMITTERS AND IMMUNITY: 1. DOPAMINE

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INTRODUCTION

Dopamine is one of the principal neurotransmitters in the central nervous system (CNC), and its neuronal pathways are involved in several key functions such as behavior (Hefco et al., 2003a,b), control of movement, endocrine regulation, immune response (Fiserova et al., 2002; Levite et al., 2001, Hritcu et al., 2006a,b,c), and cardiovascular function. Dopamine has at least five G-protein, coupled receptor subtypes, D1-D5, each arising from a different gene (Sibley et al., 1993). Traditionally, these receptors have been classified into D1-like (the D1 and D5) and D2-like (D2, D3 and D4) receptors subtypes, primarily according to their ability to stimulate or inhibit adenylate cyclase, respectively, and to their pharmacological characteristics (Seeman et al., 1993). Receptors for dopamine (particularly of D2 subclass) are the primary therapeutic target in a number of neuropathological disorders including schizophrenia, Parkinson’s disease and Huntington’s chorea (Seeman et al., 1987). Neither dopamine by itself, nor dopaminergic agonists by themselves, has been shown to activate T cell function. Nevertheless, lymphocytes are most probably exposed to dopamine since the primary and secondary lymphoid organs of various mammals are markedly innervated, and contain nerve fibers which stain for tyrosine hydroxylase (Weihe et al., 1991), the enzyme responsible for dopamine synthesis. Moreover, cathecolamines and their metabolites are present in single lymphocytes and in extracts of T and B cell clones, and pharmacological inhibition of tyrosine hydroxylase reduces catecholamine levels, suggesting catecholamine synthesis by lymphocytes (Bergquist et al., 1994). The existence of putative dopamine receptors of D2, D3, D4 and D5 subtypes on immune cells has been proposed of several authors, primarily on the basis of dopaminergic ligand binding assays and specific mRNA expression as monitored by reverse transcription-PCR. Several experiments evoked the idea of a role for dopamine in modulating, mainly suppressing immune functions (Qui et al., 1994). Animals treated with bromocriptine, a dopamine agonist, also showed suppression of antibody production to SRBC and LPS (Besedovsky and del Ray, 1996) and suppressed activities of lymphocytes in mixed lymphocyte culture (Hiestand et al., 1986). Moreover, the interest regarding the role of dopamine on immune system becomes more relevant when some of important neurological disease like Parkinson’s disease and schizophrenia with hypo- and hyperactivity (Birtwistle et al., 1988) of central dopamine system are well-correlated with severe abnormalities of immune functions (Muller et al., 1993). Therefore, in the present review, we have evaluated information from our laboratory as well as from others regarding the role of dopamine on immune function in both human and experimental animals in order to understand the current status of dopamine-mediated control of the immunological surveillance system.

DOPAMINE AND IMMUNE RESPONSE

1. Correlation between brain dopamine and immune response in pathophysiological conditions

Degeneration of nigrostriatal dopaminergic neurons in the cause of Parkinson’s disease, resulting in hypodopaminergic activity of the central nervous system (CNS) (Temlett, 1996). On contrary, in schizophrenia, a hyperdopaminergic activity has been emphasized (Birtwistle and Baldwin, 1998). Moreover, considerable evidences have also been accumulated, suggesting that both of these neurological disorders involving CNS dopaminergic system are associated with significant alterations in immune response.

In patients, with Parkinson’s disease, there was a significant reduction in the proliferative response of peripheral lymphocytes to ConA, PHA, PWM and decreased antibody production. These patients also had a decease number of CD4+ lymphocytes in their blood. This disease was also reported to be associated with reduced killer cell activity (Fiszer et al., 1991; Bokor et al., 1992). Although some results from schizophrenic patients were contradictory (Sperner-Unterweger et al., 1992), majority of the evidences indicated an immune stimulation like increase in the number of CD4+ T-lymphocytes (Muller et al., 1993; Ganguli et al., 1995). In addition, increased plasma level of interleukin (IL)-6 was also observed in schizophrenic patients (Maes et al., 1995). In some other studies, abnormal functions of T-cell-mediated-immunity, as evidenced from deficient production of IL-2 and IL-6 and elevated level of soluble IL-2 receptors, were demonstrated (Arolt et al., 1997). Immunosuppression in this schizophrenic patient may be due to the fact that probably many of these patients included in the study were treated with neuloleptics which, in turn, may have immunosuppressive effects through suppression of IL-6 or IL-6R-related mechanisms (Maes et al., 1995).

Animal studies from our laboratory showed that sulpiride-induced D2 dopamine receptor blockade was well correlated with significant depression of immune responsiveness (Hritcu et al., 2006a,b).

2. Pharmacological manipulation of CNS dopamine and immunity

Receptors for dopamine (particularly of D2 subclass) are the primary therapeutic target in a number in a number of neuropathological disorders including schizophrenia, Parkinson’s disease and Huntington’s chorea (Seeman et al., 1987), and are well-associated with severe abnormalities of immune system functions. Results from our laboratory

also support the abovementioned hypothesis of brain dopaminergic-mediated regulation on immune functions. Results indicated that sulpiride-induced D2 dopamine receptor blockade is correlated with decrease of immune response in restraint stressed rats (Hritcu et al., 2006a,b). Other experimental evidences also showed that intraventricular injection of 6-hydroxydopamine (6-OHDA) in mice, which depleted both dopaminergic and noradrenergic neurons in the CNS, resulted in an impaired primary antibody response to sheep red blood cells and activation of splenic suppresser T-cell (Cross et al., 1987). Nistico et al. (1994) also showed that stimulation of D1 dopamine receptors in different regions of the dopaminergic pathways of the brain was followed by either stimulation or inhibition of NK cell activity. Similar modulation of lymphocyte proliferation and NK cell activity was observed following lesioning of nigrostriatal and mesolimbic dopaminergic system. Interestingly, Neveu et al. (1992) and Delaplanque et al. (1992) reported that central dopaminergic pathways were asymmetrically involved in modulation of immune activity. They observed that after 6-OHDA-induced lesion of the striatum in mice, proliferation of the splenic lymphocyte was impaired only in left-lesioned group. In our laboratory, we observed that after right-unilateral 6-OHDA-induced lesioned of substantia nigra pars reticulata, the immune response of rats was influenced (Hritcu et al., 2006c). These results thus indicate bi-directional signaling between the brain monoamines and the immune system (Qiu et al., 1996).

Since dopamine cannot cross the blood-brain barrier, the specific correlation between brain dopamine and immune system is not clear. However, some of the proposed mechanisms are: a) altered central dopamine level may influence the synthesis and release of other neurochemicals which are immunomodulatory in nature. In mice, brain dopamine depletion by MPTP (1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine) showed significant increase of met-encephalin like immunoreactive and pro-encephalin mRNA content in the striatum. Intraventricular injection of met-encephalin was reported to suppress several immune parameters like antibody production, delayed hypersensitivity and CD4+ cells (Jankovic and Maric, 1990); b) hormonal regulation of immune system is well known. This is primarily achieved through the hormonal receptors present on the surface or cytoplasm of the effector cell of the immune system (Bost, 1988). Dopamine is also known t influence the release and synthesis of several anterior pituitary hormones (Ganong et al., 1985), which, in turn, can modulate the immune system.

3. Peripheral dopamine and immunity

Neurotransmitters and cytokines are the potential signaling molecules between peripheral sympathetic nervous system and the immune system. Among these mediators, dopamine is now considered to play a pivotal role in neuroimmune communication. Evidences have been discussed in support of the immunomodulatory role of peripheral dopaminergic system, the existence of which was suggested by Kopin (1985).

4. Physiologycal level of dopamine

In most mammalian species including human, the major portion of the dopamine circulates in conjugated form either as sulfoconjugate or glycoconjugate and serves as a reserve pool for the active form pM (Cuche et al., 1990). In comparison to the number of studies carried out to determine the physiological concentration of dopamine in different brain regions, little information is available regarding its circulating plasma level in health and disease states. Available information showed circulating dopamine to be 10.46 (Cuche et al., 1990) and 8.08 pM/ml (Lechin et al., 1990) whereas in synapse, it was reported to be 0.3-1 mM (Offen et al., 1995) in normal healthy individuals. No significant differences of catecholamine levels were observed in normal male and female subjects.

5. Functional significance of intracellular dopamine in immune-competent cells

The presence of intracellular dopamine in lymphocytes and neutrophils is of significance since dopamine receptors on human and murine T- and B-cells have been established (Ricci and Amenta, 1994). The synthesis and release of dopamine by lymphocytes suggest the regulation of the functional activities of these cells as an autocrine regulatory mechanism or from non-immune tissues as a paracrine mechanism (Bergquist et al., 1998).

6. Dopamine receptor expression in lymphocytes

The presence of multiple classes of dopamine receptors in the CNS was first proposed by Kebabian and Calne (1979). They classified dopamine receptors into D1 which stimulated adenylate cyclase and D2 which was independent of such coupling in the effector cells. This dual receptor concept was recognized for a long time until gene-cloning techniques demonstrated three more receptor subtypes, D3 (Sokoloff et al., 1990), D4 (Van Tol et al., 1992) and D5 (Sunahara et al., 1991). Moreover, on the basis of pharmacological, structural and biochemical studies, these receptor subtypes fall into one of the two initially recognized categories. Depending on the transmembrane homology, D1 and D5 receptors were grouped together and placed into the category known as D1 type. Similarly, D2, D3 and D4 receptors were placed into D2-like category (Missale et al.., 1998). Besides its role in cardiovascular and renal systems in the periphery, the presence of dopamine receptors in mammalian lymphocytes was first demonstrated by Le Fur et al. (1980a) who initiated the concept of dopamine as a regulator of functional activities of immune effector cells. However, this concept was strengthened only after radioligand binding and mRNA expression studies have revealed the presence of D1, D2, D3, D4 and D5 receptors on murine and human lymphocytes (Caronti et al., 1998) (Table 1).

Table 1

Dopamine receptor expression in human and murine leukocytes
PBL: peripheral blood lymphocytes.

Cell type	Host	Dopamine receptors					Methods	Reference
		D1-like		D2-like				
		D1	D5	D2	D3	D4		
T and B cells	Human					+		Radioligand Sambrogio et al. 1993
PBL	Human				+			Radioligand Ricci and Amenta 1994
PBL	Human						+	Radioligand Ricci et al. 1995
PBL	Human						+ +	Radioligand Ricci et al. 1998
PBL (nested PCR)	Human							+ mRNA Bondy et al. 1996
Lymphocytes PCR)	Rat		+		+		+	mRNA (RT Caronti et al. 1998
Lymphocytes	Human		+					Radioligand Ricci et al. 1999

However, in other studies, Vile and Strange (1996) failed to detect any D2-like dopamine receptors, on human lymphocytes. The expression of dopamine receptors on lymphocyte membrane was also found to be significantly decreased in some pathological conditions like Parkinson’s disease (Le Fur et al., 1980b), malignant tumors in mice (Basu et al., 1993) and was found to be increased in migraine (Barbanti et al., 1996). Similarly, age-dependent decrease in dopamine receptor expression has also been reported (Barili et al., 1996). Interestingly, lymphocytes from patients suffering from Parkinson's disease and malignant tumors in animals showed significant depression of their functional activities (Basu et al., 1995). However, any direct correlation between dopamine receptor expression in lymphocytes and their immune response has not yet been demonstrated. Although no direct evidence of the presence of dopamine receptors is available in macrophages and NK cells, however, treatment with different dopamine receptor agonists and antagonists can alter their functional activities (Tsao ct al., 1998). In brain, however, the biological significance of some specific classes of dopamine receptors has been well-documented with the help of transgenic mice deficient in the expression of a specific class of dopamine receptor subtype. Disruption of the D1 receptor gene showed locomotor hyperactivity in mutant mice (Xu et al., 1994), and inactivation of D2 receptor gene produced almost the opposite phenotype. These D2 receptor-deficient mice were akinetic and bradykinetic with significantly reduced spontaneous movement (Baik et al., 1995). However, the physiological significance of other dopamine receptors is yet to be ascertained. Similar techniques can be used in the future to elucidate the physiological significance of the presence of dopamine receptors in immune effector cells.

7. Dopamine and hematopoiesis

The regulation of hematopoietic system is achieved at three steps: 1) at the cellular level of bone marrow stroma, 2) at the humoral level by cytokines, and 3) by catecholamines and other neuroendocrine factors. Sympathetic nerve endings and bone marrow cells are the main source of bone marrow catecholamines (Maestroni, 1998). Among the catecholamines, substantial amount of dopamine was detected in bone marrow (Marino et al., 1997). Interestingly, in murine hosts, noradrenaline and dopamine showed a rhythmicity of levels in bone marrow with peak values observed during night. This rhythm could also be disrupted by chemical sympathectomy, thereby indicating the possible role of this daily rhytmicity in the regulation of hematopoiesis (Maestroni et al., 1998). Exogenous administration of dopamine or its analog, 3,4-dihydroxy-benzylamine, stimulated erythropoiesis and platelet production in both normal and tumor-bearing mice (Lahiri et al., 1990). In accordance with these findings indicating the role of dopamine in erythropoiesis, Idova et al. (1998) suggested increased CD4+ T-helper cells in bone morrow of aggressive mice due to activation of dopaminergic system.

8. Effect of dopamine in vivo and in vitro on functional activities of immune effector cells

Several experiments results from both human and murine hosts are now available indicating the regulatory role of dopamine on the functional activities of immune effector cells like different subsets of lymphocyte population, neutrophils, macrophages and NK cells. Results are summarized as follow.

8.1. Lymphocytes

It has already been discussed that human and murine lymphocytes as well as T- and B-cell hybridomas contain substantial amount of dopamine (Bergquist et al., 1998), and the significance of this endogenous dopamine has been proposed to be the regulator of cell proliferation. Several in vitro experiments on the effects of dopamine on murine and human lymphocytes have shown significant inhibition of lymphocyte proliferation. Cook-Milles et al. (1995) suggested that proliferation of murine spleen and thymus cells was inhibited by dopamine (10^{-4}-10^{-5} M) and the generation of reactive oxygen metabolites due to auto-oxidation of dopamine ultimately inhibited proliferation. Similar results were also suggested by Offen et al. (1995) and Josefsson et al. (1996) who reported apoptotic death of mouse thymocytes ands splenocytes in vitro. However, physiological concentration present at the synapse (0.1-0.3 mM) was used in vitro studies by Offen et al. (1995). Bergquist et al. (1997) also suggested dopamine-induced apoptotic death of both human T- and B-lymphocytes by induction of *BCL-2/BAX-2* and *Fas/FasL* genes. It is to be noted here that none of the authors used the normal physiological concentration of plasma dopamine level for their experiments. Even the immediate precursor of dopamine, L-dopa, also showed similar inhibition of lymphocyte proliferation (Slominski and Goodman-Snitkoff, 1992). Furthermore, dopamine-induced inhibition of T-cell clone, CTLL-2 and B cell lymphoma, B9 cells, strongly indicates direct inhibitory property of dopamine on these cells (Josefsson et al., 1996). Auto-oxidation of dopamine, generation of reactive oxygen metabolites, and coupling of these products to cellular protein were suggested to be the underlying mechanisms of dopamine-induced cell proliferation (Graham et al., 1978). The involvement of dopamine receptors in these dopamine-mediated proliferation inhibitions of lymphocytes was also shown to be another possibility by Morikawa et al. (1994). They showed that the activities of both resting, activated human T-cells and antibody production could be suppressed significantly in vitro by a dopamine receptor agonist, bromocriptine.

8.2. Polymorphonuclear leukocytes

Uptake, storage, synthesis of catecholamines, especially dopamine in neutrophils and its release lend support to the hypothesis of dopaminergic regulation of neutrophil functions (Cosentino et al., 1999). Some experiments also showed direct effects of dopamine on neutrophil functions. In mice, 6-OHDA induced sympathectomy, which depleted noradrenaline and dopamine, and enhanced phagocytic activity of neutrophils in mice (Derevenco et al., 1992), indicating functional suppression of neutrophils by dopamine. Other in vitro studies showed that plasma therapeutic concentration of dopamine (150 µg/ml) in culture inhibited phagocytic response of polymorphonuclear leukocytes to bacterial pathogens (Wenisch et al., 1996). Similar results were also demonstrated by Matsuoka (1990) who showed that therapeutic dopamine plasma level (837.5 ng/ml) in sick children could inhibit the respiratory bursts of these cells in vitro. Although dopamine receptors have not been directly detected in neutrophils, however, bromocriptine, a dopamine D1 receptor agonist, inhibited the release of tumor necrosis factor α (TNF-α) from neutrophils (Meli et al., 1997), indicating the possible role of dopamine receptors in these cells.

Animal studies from our laboratory showed that sulpiride-induced D2 dopamine receptor blockade was well correlated with significant decrease of neutrophils number (Hritcu et al., 2006a).

9. Effect of immune system on brain dopaminergic system

The accumulated evidences so far clearly indicate the influence of central and as well as peripheral dopaminergic system on the immune system. Since it has been proposed that brain and immune system interact with each other to maintain the homeostatic condition (Ader et al., 1995), it is therefore essential to discuss the relevant information on the influence of the immune system on central dopaminergic functions. The immune system exerts its influence on CNS through some soluble mediators like cytokines. These cytokines are low molecular weight proteins secreted from lymphoid or non-lymphoid cells mediating cell growth, inflammation, immunity, differentiation and repair. Among the different cytokines, some of the ILs and TNFs play a significant role in the regulation of central dopaminergic system. Transforming growth factor TGF α is neurotrophic for midbrain dopaminergic neurons in vitro. Blum (1998) reported that TGF-α is required for the normal proliferation or differentiation of a select population of neurons within the substantia nigra. Krieglstein et al. 1998 reported that TGF-β is required for mediating the survival-promoting effect of fibroblast growth factor-2 on dopaminergic neurons in the presence of glial cells. Intracerebral injection of IL-1 increased the brain dopamine turnover (Dunn, 1994). Similarly, IL-2 in physiological concentration stimulated the release of dopamine from neuronal cells in vitro in a dose-dependent manner (Alonso et al., 1993), thereby indicating an important physiological role of IL-2 in central dopaminergic function. Moreover, striatal and prefrontal dopaminergic functions were also altered following administration of IL-2 (Zalcman et al., 1994). Among the other cytokines, IL-6 also showed similar stimulatory effect on dopaminergic neurons in vitro by releasing dopamine (Hama et al., 1991) and in vivo by enhancing dopamine turnover in prefrontal cortex (Zalcman et al., 1994). There are also reports which showed significant increase in dopamine concentration in the hypothalamus of animals pre-treated with IL-1 β and IL-1 α (Yang et al., 1999).

10. Future scop

The immunomodulatory role of dopamine has now been emphasized, indicating that this monoamine neurotransmitter is one of the important mediators of neuroimmune interactions. Auto-oxidation of dopamine and generation of free radicals have been considered to be essential for dopamine-mediated immune suppression. However, the role of dopamine receptors and its intracellular signaling in the regulation of functional activities of different immune

effector cells cannot be ruled out as dopamine receptors are present on these cells. Moreover, modulation of the functional activities of these receptors by different dopamine agonists or antagonists has been established. Therefore, the dopamine-mediated molecular mechanisms of immune cell regulation should be evaluated in details in order to devise possible therapeutic interventions in the future by targeting dopamine receptor and its signaling pathways in immune-competent cells for the treatment of immunological disorders.

The role of DA in hematopoiesis and leukocyte trafficking is also an important aspect to be evaluated. Some basic information of this area of research, which has already been discussed, is highly encouraging in relation to the regulatory role of dopamine on these two important facets of immune system. Identification of specific DA receptors on the progenitors of the immunocompetent cells and their role in differentiation, maturation and trafficking of these cells to lymphoid organs or target sites will be of fundamental, as well as of clinical, significance. Stimulation or inhibition of functional activities of different immune-competent cells following dopamine treatment, depending on in vivo or in vitro exposure, appears to be very interesting from the pharmacological aspect of study. Although several explanations are now available in favor of immune suppression following physiological concentration of dopamine, there are no such reports yet available, which can explain the stimulation of these cells by pharmacological doses of dopamine in vivo. It will therefore be pertinent to investigate the pharmacological effects of dopamine and their mechanisms on immunity in vivo in order to assess a possible new therapeutic role of dopamine in the treatment of immunological abnormalities. Interestingly, a clinical trial with a D2 receptor agonist, lisuride, appeared to be immunologically rejuvenating in some human subjects (Poehlau et al., 1994). Dopamine-mediated autocrine, as well as paracrine, regulation of leukocyte function is also a newly emerging area of research to find out the dopamine-operated regulatory switch for immune-competent cells. Since different cytokines like IL-2, IL-6 and TNF-α have significant effects on central dopaminergic system, their effects on dopamine receptor expression and as well as their functional activities should be monitored in order to acquire in-depth knowledge regarding the molecular basis of dopamine-mediated neuro-immune interactions.

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