

Dopaminergic Regulation of Innate Immunity: a Review

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Abstract Dopamine (DA) is a neurotransmitter in the central nervous system as well as in peripheral tissues. Emerging evidence however points to DA also as a key transmitter between the nervous system and the immune system as well as a mediator produced and released by immune cells themselves. Dopaminergic pathways have received so far extensive attention in the adaptive branch of the immune system, where they play a role in health and disease such as multiple sclerosis, rheumatoid arthritis, cancer, and Parkinson's disease. Comparatively little is known about DA and the innate immune response, although DA may affect innate immune system cells such as dendritic cells, macrophages, microglia, and neutrophils. The present review aims at providing a complete and exhaustive summary of currently available evidence about DA and innate immunity, and to become a reference for anyone potentially interested in the fields of immunology, neurosciences and pharmacology. A wide array of dopaminergic drugs is used in therapeutics for non-immune indications, such as Parkinson's disease, hyperprolactinemia, shock, hypertension, with a usually favorable therapeutic index, and they might be relatively easily repurposed for immune-mediated disease, thus leading to innovative treatments at low price, with benefit for patients as well as for the healthcare systems.

Keywords Dopamine · Dopaminergic receptors · Innate immunity · Human disease · Drug repurposing

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Introduction

Dopamine (DA) is a central nervous system (CNS) neurotransmitter involved in the control of several key functions, such as cognition, motivation, movement and reward (Feldman et al. 1997). Interestingly, a key role for the reward system in the regulation of immunity has been recently highlighted, as it was shown that in mice the host defense against *E. coli* involved increased activity of the dopaminergic neurons of the Ventral Tegmental Area, a pivotal component of the reward system and induced the activation of both innate and adaptive immunity (Ben-Shaanan et al. 2016). In contrast, Cao and Aballay (2016) found that in the CNS the DA antagonist chlorpromazine results in protection against *C. elegans* infection while treatment with DA leads to increased susceptibility to *P. aeruginosa* (Cao and Aballay 2016).

DA is also present in peripheral tissues, where it affects blood pressure, sodium balance and adrenal and renal functions (Tayebati et al. 2011; Jose et al. 2003), as well as glucose homeostasis and body weight (Rubí and Maechler 2010). DA is however increasingly considered as a key transmitter between the nervous system and the immune system as well as a mediator produced and released by immune cells themselves (Basu and Dasgupta 2000; Sarkar et al. 2010; Levite 2012). Virtually all human immune cells can be affected by DA, and at least lymphocytes and dendritic cells have been reported to produce DA which in turn may act as autocrine/paracrine mediator on immune cells as well as on neighboring cells (Cosentino et al. 2007; Nakano et al. 2009).

The role of dopaminergic pathways has been so far, the subject of intense investigation in the adaptive branch of the immune system (Basu and Dasgupta 2000; Sarkar et al. 2010; Levite 2012), and their contribution has been established in human disease such as multiple sclerosis (Cosentino and Marino 2013; Marino and Cosentino 2016), rheumatoid arthritis

(Capellino et al. 2010; Nakano et al. 2011), and Parkinson's disease (González et al. 2013; Kustrimovic et al. 2016).

Comparatively little is known about dopaminergic modulation of the innate immune response, although experimental evidence supports the ability of DA to affect innate immune system cells such as dendritic cells, macrophages, microglia, and neutrophils (Sarkar et al. 2010; Levite 2012).

The present review aims at providing a complete and exhaustive summary of currently available evidence about DA and innate immunity, thus providing a reference for anyone potentially interested in the fields of immunology, neurosciences and pharmacology. Actually, a wide array of dopaminergic drugs is currently used in therapeutics for non-immune indications (Table 1) with a usually favorable therapeutic index, and they might be relatively easily repurposed for immune-mediated disease, possibly leading to innovative treatments at low price, which would benefit patients as well as the healthcare systems (Cosentino and Marino 2016).

Physiology and Pharmacology of Dopaminergic Pathways

DA is synthesized from the precursor l-dihydroxyphenylalanine (l-DOPA) and in turn can be converted to norepinephrine or epinephrine (Fig. 1). DA in human tissues can originate, not only from endogenous biosynthetic pathways, but also from many types of food (Kulma and Szopa 2007); indeed, several studies analyzed the content of DA in different fruits and vegetables and featured its antioxidant effects, comparable to those of the additives such as glutathione or butylated hydroxytoluene used in the food industry. The fruits with the highest concentrations of DA are bananas (around 42–55 µg/g). Avocado, cocoa bean powder, broccoli and bruxelle sprouts containing moderate amounts of DA (7 µmol/kg); fruits and vegetables such as tomatoes, kiwi, pineapple, potatoes and peanuts, contain very low levels of DA, less than 7 µmol/kg (Feldman et al. 1987; Kulma and Szopa 2007). It should however be emphasized that DA introduced with food is unable to cross the blood brain barrier, and it is unclear whether intestinal absorption actually provides relevant concentrations of DA in peripheral tissues. In this regard, a pharmacokinetic study in dogs, showed that the absolute bioavailability of an aqueous solution with 100 mg of DA after oral administration was only of 3% (Murata et al. 1988).

A plant remarkable for its possible applications in the clinic is *Mucunia pruriens*, a tropical plant that is typically used as fodder and becomes edible for humans after cooking. The plant, and above all the seeds, is rich in l-DOPA, the precursor of DA, and it could be a viable alternative for patients with Parkinson's disease who live in tropical areas and for whom the cost of treatment with l-DOPA is above their possibilities. Nevertheless, further studies are still necessary to characterize side effects of the plant extracts and possible interactions with other medications (Cassani et al. 2016).

The range of DA concentration in plasma of a healthy adult subject is highly variable. Eichler et al. (1989) reported values of 0.005527–0.527 nM. Eisenhofer et al. (2005) studied nine patients with DA-producing paragangliomas, reporting a concentration range of DA between 0.08 and 5.679 nM. Recently, Kustrimovic et al. (2016) reported that plasma DA was 3.2 ± 5.7 nM in healthy subjects, 2.7 ± 3.3 nM in Parkinson's disease patients without dopaminergic substitution therapy ($P = 0.779$ vs healthy subjects), and 8.0 ± 9.8 nM in Parkinson's disease patients on dopaminergic substitution therapy ($P = 0.003$ vs healthy subjects).

The gastrointestinal tract has been suggested as the major source of peripheral DA (Eisenhofer et al. 1997). Indeed, in the periphery, DA can be produced at least by three different sources, namely the neuroendocrine cells, the adrenal glands and the neuronal fibers and DA content is correlated with several functions, such as the secretion of insulin by β cells, the homeostasis of sodium at the level of kidneys, the inhibition of the secretion of von Willebrand factor and the decrease of vascular permeability (Rubí and Maechler 2010). More recently it was hypothesized that, an increase in the dopaminergic neurotransmission in the striatum may represent a risk factor for the onset of obesity; in fact, the immoderate consumption of carbohydrates stimulates the production and use of DA in the brain (Blum et al. 2014). Obesity however can also be related to dysfunction of the peripheral dopaminergic system (Rubí and Maechler 2010; Leite et al. 2016).

Immune cells themselves may however produce and release DA (Cosentino et al. 2002, 2005, 2007). In particular, treatment of lymphocytes with IFN- β leads to increased production and release of DA (as well as of norepinephrine and epinephrine) (Cosentino et al. 2005). DA content may differ in distinct lymphocyte subsets. For instance, CD4 + CD25- T lymphocytes were shown to contain on average 0.22 pM while CD4 + CD25+ regulatory T cells 37.43 pM (Cosentino et al. 2007). Besides by IFN- β , the release of DA from lymphocytes may be also induced by high K^+ (Cosentino et al. 2003).

It might then be possible that, although plasma DA is present in the nM range, in particular situations or specific micro-environments, such as at level of some cells or in the niche of a tumor, DA levels can greatly increase. It was also shown that the noradrenergic sympathetic fibers which extensively innervated the spleen, are able to release in the small volume of the varicose axon terminal, high amount of DA and a so high concentration, in such a small area, may exert an immunomodulatory effect on splenocytes (Bencsics et al. 1997).

Dopaminergic Receptors

DA exerts its effects through the interaction with dopaminergic receptors (DR), which are 7-transmembrane, G protein-coupled receptors. DR are classified into D₁-like (D₁ and

Table 1 Pharmacological characteristics of dopamine and dopaminergic agonists and precursors

ATC ¹	name	main therapeutic indications ²	pharmacology ³
<i>dopamine precursors</i>			
N04BA01	levodopa	Parkinson's disease and related conditions	dopamine precursor
N04BA04	melevodopa	Parkinson's disease and related conditions	dopamine precursor
N04BA06	etilevodopa	Parkinson's disease and related conditions	dopamine precursor
<i>dopamine and dopamine analogues</i>			
C01CA04	dopamine	shock (cardiogenic post-infarct, surgical, hypovolemic, hemorrhagic, septic, anaphylactic)	agonist at D ₁ -like/D ₂ -like DR
C01CA14	dopexamine	inotropic agent, reduction of heart failure, treatment of heart failure following cardiac surgery	agonist at D ₁ -like/D ₂ -like DR and at β ₂ -AR
<i>dopamine agonists</i>			
C01CA16	ibopamine	mydriatic (not cycloplegic)	agonist at D ₁ -like DR and at α-AR
C01CA19	fenoldopam	iv emergency treatment of hypertension	agonist at D ₁ -like DR D ₁ , weak agonist at D ₂ -like DR D ₄ and at α ₁ - and α ₂ -AR
G02CB01/N04 BC01	bromocriptine	Parkinson's disease and related conditions, hyperprolactinemia	agonist at D ₂ -like DR D ₂ and D ₃ , agonist at several 5-HT receptors, and at α ₁ - and α ₂ -AR
G02CB02	lisuride	Parkinson's disease and related conditions, hyperprolactinemia, migraine prophylaxis	agonist at D ₂ -like DR D ₂ , D ₃ and D ₄ , agonist at some 5-HT receptors
G02CB03/N04 BC06	cabergoline	Parkinson's disease and related conditions, hyperprolactinemia, uterine fibroids, acromegaly (adjunctive therapy)	agonist at D ₂ -like DR D ₂ and D ₃ , weak agonist at some 5-HT receptors, and at α ₁ - and α ₂ -AR
G02CB04	quinagolide	hyperprolactinemia	agonist at D ₂ -like DR
G02CB05	metergoline	hyperprolactinemia, migraine prophylaxis	similar to bromocriptine
G02CB06	terguride	hyperprolactinemia, pulmonary arterial hypertension (orphan drug status)	agonist/antagonist at D ₂ -like DR, partial agonist/antagonist at several 5-HT receptors, antagonist at α ₂ -AR
N04 BC02	pergolide	Parkinson's disease and related conditions ^a	agonist at D ₁ -like/D ₂ -like DR as well as at several 5-HT receptors
N04 BC03	dihydroergocryptine	Parkinson's disease and related conditions, migraine prophylaxis, low blood pressure in the elderly, peripheral vascular disorders	agonist at D ₂ -like DR
N04 BC04	ropinirole	Parkinson's disease and related conditions, moderate-to-severe primary restless legs syndrome	agonist at D ₂ -like DR D ₂ , D ₃ and D ₄
N04 BC05	pramipexole	Parkinson's disease and related conditions, moderate-to-severe primary restless legs syndrome	agonist at D ₂ -like DR D ₂ , D ₃ and D ₄
N04 BC07	apomorphine	Parkinson's disease and related conditions, erectile dysfunction, alcoholism and opioid addiction	agonist at D ₂ -like DR D ₂ , D ₃ and D ₄
N04 BC08	piribedil	Parkinson's disease and related conditions	agonist at D ₂ -like DR D ₂ and D ₃ , antagonist at α ₂ -AR
N04 BC09	rotigotine	Parkinson's disease and related conditions, moderate-to-severe primary restless legs syndrome	agonist at D ₁ -like/D ₂ -like DR

1 = from the ATC/DDD Index of the WHO Collaborating Centre for Drug Statistics Methodology - <http://www.whocc.no/>, 2 = from the AIFA Medicines Database - <https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home>, 3 = from <http://www.guidetopharmacology.org/PDSP> Ki database and <http://kiddbdev.med.unc.edu/databases/kiddb.php/>, a = withdrawn from the US market for human use after published evidence linking the drug to increased rates of valvular heart disease <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051285.htm>; <http://web.archive.org/web/20070408111551/http://www.fda.gov/cder/drug/advisory/pergolide.htm>

D₅, previously known as D_{1a} and D_{1b}), located both pre- and post-synaptically and D₂-like (D₂, D₃ and D₄), that are mainly post-synaptic (Andersen et al. 1990; Sibley et al. 1993; Jaber

et al. 1996; Beaulieu and Gainetdinov 2011). D₁-like family activates G_{αs/olf} proteins to stimulate cyclic adenosine monophosphate (cAMP) production by adenylyl cyclase (AC),

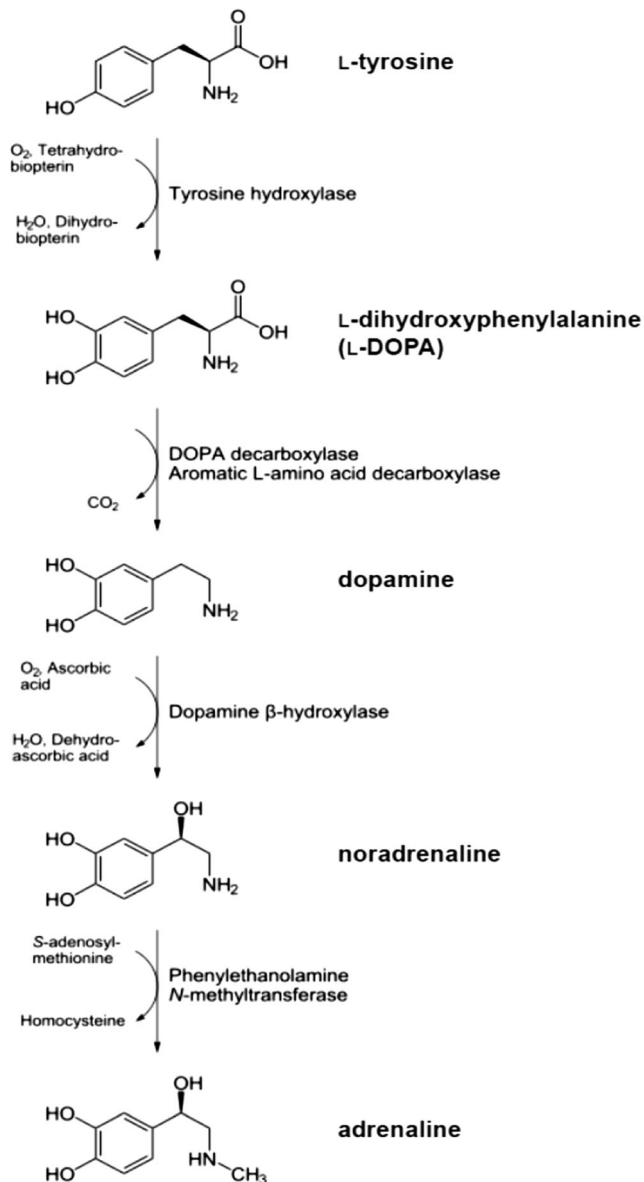


Fig. 1 Biosynthetic pathway of the catecholamines dopamine, noradrenaline and adrenaline from the amino acid tyrosine. The synthesizing enzymes are shown to the right of each arrow, while enzyme cofactors are shown to the left (reproduced from the Wikimedia Commons- <http://commons.wikimedia.org>)

whereas D_2 -like family stimulates $G_{\alpha i/o}$ proteins, which inhibit AC, resulting in reduced cAMP levels (Beaulieu et al. 2015). D_1 -like DR may also increase intracellular calcium levels while D_2 -like DR, particularly DR D_3 and DR D_4 , may have opposite effects (Missale et al. 1998).

The DR D_2 receptor exists in two different isoforms: short (S) and long (L), generated by the alternative splicing of an exon and located, respectively, pre- and post-synaptically (Missale et al. 1998; Lindgren et al. 2003). The DR D_2L has 29 additional amino acids in the third intracellular loop, resulting in a different affinity for G proteins (Usiello et al. 2000). DR D_2 is the main target for several neuroleptic drugs.

In particular, it was shown that the action of one of the most common of these drugs, haloperidol, is mediated by the long isoform, as mice deficient for DR D_2L lack the cataleptic effect due to haloperidol. The main role of the short form, which is localized at the pre-synaptic level, seems to be the interference with DR D_1 signaling (Usiello et al. 2000).

DR may also form oligomeric complexes together with other DR or with different receptors (Perreault et al. 2014). The most extensively characterized allosteric interaction is between DR D_2 and the adenosine A_2A receptor (A_2AR) (Fuxe et al. 2005; Casadó-Anguera et al. 2016). This heteromer has been described in neurons and it has been suggested to mediate the depressant effects of adenosine analogues and the psychostimulant effects of adenosine antagonists such as caffeine. It is also implicated in several neuropsychiatric disorders (Bonaventura et al. 2015; Ferrè et al. 2016).

DR D_2 may also form heteromers with the 5-HT receptors 5-HT $_{2A}$ R and 5HT $_{1A}$ R, which are presently investigated as potential targets for novel neuroleptic drugs (Albizu et al. 2011; Łukasiewicz et al. 2016). Heteromers between DR D_1 and DR D_2 have also been described, even if their actual occurrence remains controversial (Frederick et al. 2015). DR D_1 - D_2 heteromers may induce the release of intracellular calcium, resulting in the activation of striatal neurons (Hasbi et al. 2011). They might be also involved in the sensitization to cocaine (Capper-Loup et al. 2002) and have been proposed as therapeutic targets in depression, anxiety-like behaviors and schizophrenia (Shen et al. 2015). Circumstantial evidence also exists about DR D_1 - D_3 heteromers, which might have therapeutic implications in Parkinson's disease (Ferrè et al. 2010), DR D_2 - D_3 heteromers as targets for neuroleptics (Maggio and Millan 2010), and DR D_2 - D_5 heteromers which might affect calcium signaling and are possibly involved in drug addiction and schizophrenia (So et al. 2009).

No information on DR homo/etero oligomeric complexes exist in immune cells, where also the signal transduction mechanisms acted upon by such receptors remain so far ill defined.

The Innate Immune System

Innate immune cells include: granulocytes (neutrophils, eosinophils, basophils, and mast cells), monocytes/macrophages, dendritic cells, natural killer (NK) cells and innate lymphoid cells (ILC). In the CNS, innate immune responses are mediated by resident microglia, comprising perivascular and juxtavascular subsets, and astrocytes. Agents of innate immunity, besides anatomical barriers such as skin and mucosal surfaces, include effector molecules such as the complement system and antibacterial peptides, as well as several types of cells. The **complement system** is a proteolytic cascade which acts as a first-line host defense against pathogenic infections, selectively recognizing foreign pathogens and

damaged self-cells (Noris and Remuzzi 2013; Degn and Thiel 2013). **Antibacterial peptides** are cationic peptides with antibiotic and immunomodulating properties (Table 2; Boman 2003; Ganz 2003; Zanetti 2004).

Innate immune system cells express **pattern recognition receptors (PRR)**, which recognize both exogenous pathogen-associated molecular patterns (PAMP) and endogenous danger - or damage-associated molecular patterns (DAMP). PRR include: toll-like receptors (TLR, “toll” meaning in German “amazing” or “great”), NOD-like receptors (NLR, NOD meaning Nucleotide-binding Oligomerization Domain), C-type lectin receptors (CLR), RIG-I-like receptors (RLR, RIG-I meaning Retinoic acid-Inducible Gene 1), and AIM2-like receptors (ALR, AIM-2 standing for “absent in melanoma 2”, which is a protein contributing to the defense against bacterial and viral DNA). PRR may also include formyl peptide receptors (FPR, binding N-formyl peptides derived from the degradation of bacterial or host cells) and scavenger receptors (binding oxidized or acetylated low-density lipoprotein) (Kawai and Akira 2010; Takeuchi and Akira 2010, Saxena and Yeretssian 2014). Examples of PAMP and DAMP interacting with PRR are provided in Table 3 and Table 4, respectively. Among PRR, TLR and NLR are the most extensively characterized. In humans, 10 functional TLR have been identified (12 in mice, with TLR1–TLR9 being conserved in both species), which recognize microbial membrane components such as lipids, lipoproteins and proteins (TLR1, TLR2, TLR4, TLR5, TLR6, expressed on cell surfaces) and microbial nucleic acids (TLR3, TLR7, TLR8 and TLR9, expressed exclusively in the endoplasmic reticulum, endosomes,

lysosomes and endolysosomes; Kawai and Akira 2010). As for NLR, the 22 human receptors are divided into five sub-families by their N-terminal effector domains which confer unique functional characteristics. NLRA (CIITA) are transcriptional regulators of MHC class II antigen presentation. NLRB (NAIP) proteins contribute to host defense and cell survival. NLRC include NOD1 (NLRC1) and NOD2 (NLRC2), the first NLR to be identified, which sense bacterial peptidoglycan and are key players in tissue homeostasis and host defense against bacterial pathogens. The pyrin domains (PYD) containing NLRP subfamily (NLRP 1–14) have a role in inducing the inflammasome. The NLRX subfamily so far comprises only NLRX1, which may affect mitochondrial activity; however, the ~~its~~ precise role of this subfamily remains to be established (Saxena and Yeretssian 2014).

The primary function of the innate immune system is usually considered the defense of the host from infections by other organisms. In recent years, evidences were accumulated regarding its key role in noninfectious diseases like atherosclerosis (Chávez-Sánchez et al. 2014; Courties et al. 2014), cancer (Marcus et al. 2014; van den Boorn and Hartmann 2013), autoimmune diseases such as multiple sclerosis and other demyelinating diseases (Hernandez-Pedro et al. 2013; Mayo et al. 2012), systemic sclerosis (O’Reilly 2014), autoimmune uveitis (Rosenbaum and Kim 2013), lupus erythematosus (Aringer et al. 2013), neurodegenerative diseases (Boutajangout and Wisniewski 2013), gastrointestinal diseases such as inflammatory bowel disease (Levine and Segal 2013), obesity (Lumeng 2013), diabetes (Lee 2014) and liver inflammation (Meli et al. 2014; Liaskou et al. 2012). Innate immunity is also involved in preeclampsia (Perez-Sepulveda et al. 2014), organ transplantation (Farrar et al. 2013), and possibly even in psychiatric diseases (Jones and Thomsen 2013).

Table 2 Human antimicrobial peptides (based on Boman 2003, Ganz 2003, Zanetti 2004)

Name	Distribution
α-Defensins	
HNP1–3	granulocytes (spleen, thymus, lung?)
HNP4	Granulocytes
HNP5	Paneth cells of the intestine, genital tract
β-Defensins	
hBD-1	skin, lung, gut (epithelial cells)
hBD-2	skin, lung, gut (epithelial cells)
hBD-3	skin, lung, tonsils
hBD-4	testis, gastric antrum
Cathelicidin family	
LL-37 (proFALL, hCAP18)	granulocytes, lung, skin, testis, gut, lymphocytes
Saposin family	
Granulysin	cytolytic T cells, NK cells

Abbreviations: *HNP* human neutrophil peptide, *hBD* human beta defensin, *LL-37* 37-residue peptide whose N-terminal sequence is LL, *FALL* 39-residue peptide whose N-terminal sequence is FALL, *hCAP* human cationic antimicrobial protein.

Effect of DA on Innate Immune Cells

Neutrophils

Neutrophils are the first line of host defense against a wide range of infectious pathogens exerting their role in host defense through the secretion of cytokines, proteases, reactive oxygen species (ROS) generation and neutrophil extracellular traps (NET) formation (Kumar and Sharma 2010). In the past, these cells were considered as playing a role only in the early stages of acute infection, given their short lifespan, but it is now acknowledged that they can survive more than the postulated few hours and that they exert a more complex role in the communication with both the innate and adaptive immune system (Mantovani et al. 2011; Amulic et al. 2012; Kolaczowska and Kubes 2013; Pinoli et al. 2016a). Neutrophils are involved not only in the generation but also in the maintenance of in loco inflammation (Kruger et al.

Table 3 PAMP detection by TLR and other PRR (reproduced with permission from Kawai and Akira 2011)

Species	PAMP	TLR Usage	PRR Involved in Recognition
Bacteria, mycobacteria	LPS	TLR4	
	lipoproteins, LTA, PGN, lipoarabinomannan	TLR2/1, TLR2/6	NOD1, NOD2, NALP3, NALP1
	flagellin	TLR5	IPAF, NAIP5
	DNA	TLR9	AIM2
	RNA	TLR7	NALP3
Viruses	DNA	TLR9	AIM2, DAI, IFI16
	RNA	TLR3, TLR7, TLR8	RIG-I, MDA5, NALP3
	structural protein	TLR2, TLR4	
Fungus	zymosan, β -glucan	TLR2, TLR6	Dectin-1, NALP3
	Mannan	TLR2, TLR4	
	DNA	TLR9	
	RNA	TLR7	
Parasites	tGPI-mutin (<i>Trypanosoma</i>)	TLR2	
	glycoinositolphospholipids (<i>Trypanosoma</i>)	TLR4	
	DNA	TLR9	
	hemozoin (<i>Plasmodium</i>)	TLR9	NALP3
	profilin-like molecule (<i>Toxoplasma gondii</i>)	TLR11	

2015). The existence of DR on human neutrophils was initially reported in 1999 by Sookhai and co-workers, who identified, by means of immunohistochemistry, the presence of the D₁-like DR D₁ (Sookhai et al. 1999). The presence of the D₂-like DR D₂, D₃ and D₄ was subsequently reported (Pereira et al. 2003; Boneberg et al. 2006). Chen and colleagues, by means of qRT-PCR, and McKenna and colleagues, using flow cytometry, showed the presence on human neutrophil of all five DR, both at mRNA and membrane protein level (Chen et al. 2014; McKenna et al. 2002; Pinoli et al. 2016b). In

particular, it was observed that mRNA levels of DR were expressed with the following order of magnitude, D₄ > D₃ > D₁ > D₅ > D₂ (Chen et al. 2014). On the contrary, McKenna found that DR D₅ had the highest expression, whereas DR D₁ the lowest (McKenna et al. 2002).

Functional studies performed in in vitro conditions, usually report inhibitory effects of DA on several neutrophil functions as for example the inhibition of fMLP-stimulated superoxide anion production by human neutrophils (Yamazaki et al. 1989). DA has also been reported to attenuate CD11b/CD18

Table 4 DAMP interaction with TLR and NLR and their physiological effects (reproduced with permission from Tolle and Standiford 2013)

DAMP	Receptor	Effect
<i>ECM components</i>		
Fibronectin	TLR4	Increase NF- κ B, promote leukotriene synthesis and PMN migration, activate the adaptive immune system
Hyaluronan	TLR4 \pm TLR2, NLR3	Induce proinflammatory cytokines, activate DCs and macrophages
Heparan sulphate	TLR4	Increase TNF α expression, activate DCs
<i>Stress-response molecules</i>		
Heat shock proteins	TLR2, TLR4	Induce cytokines and protein kinases, activate PMNs
HMGB1	TLR2, TLR4	Induce NF- κ B nuclear translocation and cytokine expression
Nucleic acids	TLR3, TLR7, TLR9	Induce cytokine expression, activate DCs, stimulate recruitment of leukocytes and PMNs
microRNA	TLR8	Induce NF- κ B and cytokines expression
<i>Immunomodulatory proteins</i>		
β -Defensins	TLR1/TLR2, TLR4	Induce NF- κ B and cytokine expression, activate DCs and monocytes
Surfactant protein A	TLR4 \pm TLR2	Reduce NF- κ B and cytokine expression
Surfactant protein D	TLR2, TLR4	Inhibit cytokine production and recruitment of PMNs
<i>Others</i>		
Uric acid	NLR3	Increase IL-1 β expression

expression in these cells, with consequently diminished ability of human neutrophil adherence to the endothelium, as well as a decrease in the production of ROS and superoxide anions, cell migration and phagocytic activity (Wenisch et al. 1996; Sookhai et al. 2000; Matsuoka 1990; Trabold et al. 2007).

A study about the morpho-functional changes that occur in neutrophils following treatment with DA, also showed that DA increases *in vitro* neutrophil apoptosis both in healthy subjects and in patients with systemic inflammatory response syndrome (SIRS) (Sookhai et al. 1999).

It is interesting to note that in rats, dopaminergic agents are able to influence the number of neutrophils during anaphylactic shock: DA antagonists, such as chlorpromazine and pimozone, reduced neutrophil count, while agonists like apomorphine, led to an increased number of neutrophils, which is typical of conditions occurring during anaphylactic shock (Altenburg et al. 1995). Dopaminergic agonists are able to reduce the Th17-induced response and ovalbumin antigen-induced activation of neutrophils in a mouse model of airway inflammation (Nakagome et al. 2011).

It was recently reported that treatment with L-DOPA, the precursor in the synthesis of DA, led to neutropenia in a patient with Parkinson's disease. Neutrophils of the patient were shown to have reduced mRNA levels of all D₂-like DR and increased mRNA levels of tyrosine hydroxylase and DR D₅ (Cordano et al. 2015).

Eosinophils

Eosinophils are associated with allergy and asthma (Rothenberg and Hogan 2006) and exert a protective role against parasites, as highlighted by the discovery of eosinophilic granules content on helminth surface (Cadman et al. 2014).

These cells express on their membrane all the five DR (McKenna et al. 2002). Aside from this data, only a few studies are reported in literature about the ability of DA to modulate eosinophil functions. The first report comes from an *in vitro* study in rats and dates back to 1979. The study shows that treatment of animals with L-DOPA or apomorphine results in a biphasic effect on eosinophil counts. At high concentrations of both drugs, eosinophil count decreases, whereas at low concentrations, the scenario is exactly the opposite (Podolec et al. 1979). Administration of DA, in a patient awaiting heart transplant, resulted in a reduction in the explanted heart of eosinophilic myocarditis and peripheral eosinophilia (Takkenberg et al. 2004) suggesting that DA might be an additional medication in some patients awaiting transplant.

Basophils

Basophils are less than 1% of total blood leukocytes and are considered the most important cells protecting against infections of parasites (Karasuyama and Yamanishi 2014). They

produce cytokines involved in the cross-talk with the adaptive immunity, such as IL-4 (Karasuyama et al. 2011). To our knowledge, no data are present in literature about the presence of DR on these cells as well as about a possible role of DA as modulator of basophil functions.

Mast Cells

These cells, mainly present in the airways, were firstly described in the 1878 by Paul Ehrlich and are involved in most of the inflammatory processes of the respiratory system (Erjefält 2014). In mice, bone-marrow derived mast cells contain DA and express the rate-limiting enzyme TH, necessary for the biosynthesis of DA (Rönnerberg et al. 2012). Several dopaminergic agents exhibit a dose-dependent inhibition of degranulation in the mast cell line RBL-2H3, but this effect might not involve DR (Seol et al. 2004). In contrast, Mori and colleagues showed that treatment with DA induces mouse bone marrow-derived mast cell degranulation, and that a D₁-like DR antagonist reverses this effect (Mori et al. 2013).

Monocytes/Macrophages

Monocytes and macrophages, together with dendritic cells, represent the mononuclear phagocyte system, which plays a key role maintaining tissue integrity during development. Mononuclear phagocytes are also critical in tissue restoration after injury, as well as in the initiation and resolution of innate and adaptive immune responses. Due to their heterogeneity, human **monocytes** are divided in subsets based on the different stages of differentiation, size and activation. They are characterized by the expression of CD14, the LPS-receptor, and by another marker, the CD16. Monocytes in peripheral blood are usually considered as classical (CD14⁺⁺CD16⁻), intermediate (CD14⁺⁺CD16⁺) and lastly non classical monocytes (CD14⁺CD16⁺⁺) (Williams et al. 2012).

Ilya Mechnikov introduced the term **macrophage** (from Greek, “large eaters”), based on their ability to engulf microorganism and damaged tissues (Zalkind 2001). They originate from monocytes, which leave the bloodstream and undergo morpho-functional changes in response to several differentiation factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) (Parihar et al. 2010).

Several studies indicate that human monocytes express DR both at mRNA and protein level (McKenna et al. 2002; Watanabe et al. 2006; Coley et al. 2015; Gaiuzzi et al. 2016a, b). DA and dopaminergic agents can affect several functions of these cells; for example, DA is able to decrease LPS-induced proliferation of human monocytes (Bergquist et al. 2000), while the D₁-like DR agonist SKF-38393 increases CD14 + CD16⁺ monocyte chemokinesis (Coley et al. 2015). Recently, it was shown that in LPS-stimulated

bone marrow-derived macrophages, the inflammatory process is mitigated by the action of DA on DR D₁, through the inhibition of the NLRP3 inflammasome, a cytosolic protein complex that induces inflammation in response to bacterial pathogens. Moreover, DA, acting on DR D₁, can prevent systemic and neuro-inflammation also *in vivo* (Yan et al. 2015).

Monocytes oxidative burst is under an endogenous dopaminergic tone (Carvalho-Freitas et al. 2007, 2008, 2011). Monocytic cell lines, such as RAW 264.7 (a mouse cell line), contain DA (Brown et al. 2003), and, like the human cell line U937, expresses L-DOPA decarboxylase, the enzyme that converts L-DOPA into DA (Kokkinou et al. 2009). Moreover, these cells are able to produce DA: stimulation with LPS induces an increase of DA levels within 48 h (Brown et al. 2003). In addition, it has been shown that DA at high concentrations (millimolar range), increased the apoptosis of RAW 264.7 and decreased their proliferation (Brown et al. 2003). DA is also able to induce cytokine production in monocytes (Gaskill et al. 2012). Haskó and colleagues confirmed that treating mouse macrophages with DA suppresses LPS-induced IL-12p40 production (a cytokine secreted primarily by antigen-presenting cell that has a key role in determining the type of immune response to antigens). However, such effect might be mediated by adrenergic receptors (Haskó et al. 2002). DA and dopaminergic agonists are able to interfere with the production of TNF- α and nitric oxide (NO) in mouse monocytes (Haskó et al. 1996; Chi et al. 2003), and DA can also modulate the expression of surface markers in cells from guinea pigs, such as the Fc-gamma receptor, important for the host defense. Fc-gamma receptor on these cells is reduced following treatment with dopaminergic agents (Gomez et al. 1999).

In viral infections, DA may play a negative role. In fact, primary monocyte-derived macrophages (MDM) inoculated with HIV and in the presence of DA, are more susceptible to virus infection; indeed, DA increases the viral replication (Gaskill et al. 2009). This DA-dependent effect was confirmed by means of a pan-DR antagonist, flupenthixol, which abrogated the activation of DR (Gaskill et al. 2014). The same results were obtained during treatment with methamphetamine. In this case researchers observed an increase in the activity of reverse transcriptase of the virus in human macrophages that was blocked after treatment with SCH-23390 and SKF-83566, two D₁-like DR antagonists (Liang et al. 2008).

Microglia

A specialized population of macrophages resident in the CNS is microglia. Originally described in 1932 by del Rio-Hortega, these cells show a unique phenotype different from both glia and neurons (Block and Hong 2005, Kettenmann et al. 2011). Upon activation, they change their morphology from ramified to amoeboid, increase their phagocytic activity and increase

their release of pro-inflammatory mediators (Pannell et al. 2014, Nayak et al. 2014). Microglia is divided into subpopulations according to anatomical location: perivascular microglia, mainly within the basal lamina of a blood vessel and juxtavascular microglia, externally in contact with the basal lamina of the blood vessel (Gehrmann et al. 1995).

Unregulated activation of microglia can lead to neuroinflammation resulting in the neurodegeneration that occurs in several diseases (Block and Hong 2005) like Alzheimer's disease (Meda et al. 1995; Rogers et al. 2007; Li et al. 2014; Bodea et al. 2014) and Parkinson's disease (Qian and Flood 2008; Mastroeni et al. 2009; Tanaka et al. 2013; Wang et al. 2015), as well as multiple sclerosis (Li et al. 1996; Duffy et al. 2016; Raine 2016).

Cultured murine and rat glial cells express all five DR (Färber et al. 2005; Huck et al. 2015). Human elderly microglia expresses all DR with the exception of DR D₁, based on RT-PCR and immunohistochemistry studies (Mastroeni et al. 2009). DA can influence the functions of these cells attenuating the release of nitric oxide in microglia derived from mice and rats (Chang and Liu 2000; Färber et al. 2005). Moreover, DA significantly stimulated both human, mice and rats microglial chemotaxis (Färber et al. 2005; Mastroeni et al. 2009). Dopaminergic regulation of microglia has been recently revised in detail by Gaskill and colleagues (Gaskill et al. 2013).

Dendritic Cells

Dendritic cells (DC) are antigen-presenting cells and their name comes from protrusions, similar to dendrites of neurons that grow on their surface during maturation. They are divided into two major subgroups: myeloid dendritic cells, similar to monocyte, and plasmacytoid dendritic cells, which look like plasma cells (De Kleer et al. 2014). DC possess high phagocytic activity as immature cells and high cytokine producing ability as mature cells. They are able to migrate into the lymphoid organs and regulate T cell responses both in the steady-state and during infection (Mellman and Steinman 2001; De Kleer et al. 2014). DC are important for T cells activation and DA seems to play an important role in this context (Pacheco et al. 2009; Levite 2015). DR are expressed on human monocyte-derived DC and on peripheral blood DC (Nakano et al. 2008; Gaiuzzi et al. 2016b) and these cells also produce and store DA in compartments close to the plasma membrane (Nakano et al. 2009). Moreover, mouse bone marrow-derived DC express TH (Prado et al. 2012). DR expression can be modulated by different kind of stimuli. For example, Prado and colleagues found that both immature and mature mouse DC express on their surface all the DR with the only exception of DR D₄, while treatment with LPS induces a significant down-regulation of DR D₅, suggesting a role of this receptor in the cell maturation's process (Prado et al. 2012). Similarly,

treatment with D₁-like DR agonists provides improvement in a model of autoimmune disease in mice (Nakano et al. 2008).

Haloperidol, a D₂-like DR antagonist (a typical neuroleptic drug), is able to suppress murine DC maturation and to attenuate the secretion of IL-12p40, which is an important marker of cell maturation (Matsumoto et al. 2015). In human monocyte-derived DC, risperidone, an atypical neuroleptic drug acting preferentially on DR D₂, but also on 5-HT receptors, was able to modulate the production of pro-inflammatory cytokines (Chen et al. 2012).

Similarly, Nakano and colleagues report that DA present in dendritic cells is able to polarize versus Th2 differentiation while on the contrary, the result of DA depletion is the shift versus Th1 differentiation (Nakano et al., *Int Immunol.* 2009;21:645–54).

Natural Killer Cells

Natural Killer (NK) cells play an important role in innate immunity and their primary role is the killing of pathogens and protection of the organism against external invasion (Vivier et al. 2008). They show the ability to eliminate cancer cells and virus-infected cells (Moretta et al. 2014), thanks to the secretion of a large amounts of cytokines, like granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF- α , interferon (IFN)- γ , and chemokines such as CC chemokine ligand (CCL) 3, macrophage inflammatory protein (MIP)-1, CCL4 and CCL5 (Walzer et al. 2005).

DR are expressed on NK (McKenna et al. 2002; Zhao et al. 2013a; Boneberg et al. 2006) and treatment of NK cells derived from mouse spleen with SKF-38393 (D₁-like DR agonist) enhanced NK cytotoxicity, whereas quinpirole, a D₂-like DR agonist, weakened the cytotoxic activity (Zhao et al. 2013a). Spleen-derived NK of rats with a hyperactive dopaminergic system had a reduced killing capacity compared to those of hypodopaminergic rats (Teunis et al. 2004). The suppression of immune status observed after the treatment with morphine (Bayer et al. 1990; Saurer et al. 2004), was antagonized with 7-OHDPAT, a D₂-like agonist (Saurer et al. 2004). In addition, in human peripheral-blood derived NK, drugs acting as dopaminergic antagonists may inhibit NK cell responses (Theorell et al. 2014; Won et al. 1995).

Astrocytes

Astrocytes are the most abundant glial cells in the CNS (Kimelberg and Nedergaard 2010) and are divided in two main subtypes: protoplasmic astrocytes, mostly found in the grey matter, and fibrous astrocytes present in the white matter (Sofroniew and Vinters 2010). The most common marker used to identify astrocytes is the glial fibrillary acid protein (GFAP), even if they show a local and regional variability due to the action of different signaling molecules (Sofroniew and

Vinters 2010). The most important functions of these cells include the regulation of cerebral blood flow and the formation and elimination of synapses (Chung et al. 2015). They have an important role not only in physiological, but also in pathological conditions such as Rett syndrome, fragile X mental retardation, Alexander's disease and possibly in Down syndrome (Molofsky et al. 2012). This emerging role in neural circuit maturity is also linked to the development of several psychiatric and neurological disorders resulting from synaptic deficit (Seifert et al. 2006; Molofsky et al. 2012; Clarke and Barres 2013; Moraga-Amaro et al. 2014; Koyama 2015; Pekny et al. 2016).

The presence of DR on astrocytes was described in rats and monkeys, in particular for the DR D₂ (Bal et al. 1994; Khan et al. 2001). In addition, in rat astrocytes, a non-toxic concentration of DA influenced intracellular calcium signaling (Vaarmann et al. 2010) and the increase in Ca²⁺ levels occurred through the stimulation with a D₁-like DR agonist and was prevented by a dopaminergic antagonist (Liu et al. 2009; Zhang et al. 2009). Moreover, DA stimulates cAMP production in cultured striatal astrocytes of rat and DA-induced effect is mimicked by the D₁-like agonist SKF-38393 (Zanassi et al. 1999).

Effect of DA on Complement and on Antibacterial Peptides

Complement

In vitro, the complement factor C5a, which has several harmful effects during sepsis, blunted PC12 cell production of noradrenaline and dopamine, possibly inducing apoptosis in these cells. Blockade of C5a receptors might represent a promising complement-blocking strategy in the clinical setting of sepsis (Flierl et al. 2008). In a prospective randomized trial in patients undergoing coronary artery bypass grafting, the D₁-like DR agonist fenoldopam reduced the release in blood of the complement component C3a (but not of C4a and C5a) and of IL-6 and IL-8 (but not of IL-10, IL-12, and tumor necrosis factor α), suggesting that fenoldopam may induce a partial attenuation of the inflammatory response (Adluri et al. 2010).

Antibacterial Peptides

No evidence exists so far regarding any direct connection between dopaminergic pathways and antibacterial peptides. Nonetheless, it has been shown that some antibacterial peptides may display cytoprotective properties at least in vitro on dopamine-producing cells like the neuroblastoma SH-SY5Y cells (Nam et al. 2013; Kim et al. 2014). DA at high concentrations (10–100 μ M) displays significant affinity for β ₂-adrenoceptors (Katritch et al. 2009), which in turn may affect

the expression of several antibacterial peptides in many epithelia (reviewed in Scanzano and Cosentino 2015). DA therefore might contribute to the modulation of antibacterial peptide production also through adrenergic mechanisms.

Dopaminergic Modulation of Innate Immunity: Clinical and Therapeutic Relevance

Dopaminergic modulation of the immune response plays a role in several immune-mediated diseases including autoimmune disease, like multiple sclerosis (MS; Cosentino and Marino 2013; Marino and Cosentino 2016) rheumatoid arthritis (RA; Capellino et al. 2010; Nakano et al. 2011), and HIV (Gaskill et al. 2013, 2014; Williams et al. 2014). Most of the information available regard however the adaptive arm of immunity.

Peripheral immunity is also being recognized as a novel player in neuroinflammation and neurodegeneration, such as in Parkinson's disease (PD) (González et al. 2013; Kustrimovic et al. 2016), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and traumatic brain injury (TBI). However, it is presently unknown whether dopaminergic modulation of peripheral immunity has any role in disease progression and/or in the response to treatments.

Dopamine, together with noradrenaline, is the drug of choice in the treatment of septic shock, where catecholamines are used as vasopressor agents, and the relevance of their immunomodulatory potential in this context has never been assessed so far.

Immune-Mediated Diseases

Multiple Sclerosis

MS is a chronic demyelinating disease induced by an autoimmune response against constituents of the central nervous system. It affects about 2.4 million individuals worldwide and is clinically characterized by progressive loss of neurological functions due to the destruction of the sheath axonal myelin in different areas of the brain and spinal cord.

The involvement of DR-operated modulation of the immune response is well established in autoimmune diseases (Pacheco et al. 2014) and specifically in MS (Cosentino and Marino 2013; Marino and Cosentino 2016), in particular in the relapsing-remitting (RR) form (Zaffaroni et al. 2008; Cosentino et al. 2012). Among DR, evidence points to a critical role of D₁-like DR, and in particular of the DR D₅ subtype (Prado et al. 2013; Cosentino et al. 2014). Zaffaroni et al. (2008) performed a longitudinal study in RR-MS undergoing treatment with IFN- β and found that the mRNA levels of DR D₅ during 12 months of treatment in circulating lymphocytes were significantly increased and in parallel, DR D₂ mRNA levels progressively decreased. Overall, it seems that IFN-

beta shifts dopaminergic pathways in circulating lymphocytes towards a prevalent DR D₅ modulation. In contrast to extensive information about dopaminergic pathways in T lymphocytes during MS, little is known about dopaminergic modulation of innate immunity.

Monocytes and DC exert a key role in antigen presentation, promotion of inflammation and tissue damage in MS and recently the presence of DR was described in DC and monocytes of MS patients (Gaiazzi et al. 2016a, b). In a mouse model of EAE, it was shown that DC express DR D₅ which favor IL-23 and IL-12 production, contributing to CNS recruitment of pathogenic Th17 cells and disease severity (Prado et al. 2012). Monocytes appear to play a central role in MS, contributing to the breakdown of the blood-brain barrier and facilitating the trafficking of T cells within the CNS (Waschbisch et al. 2011). Among innate immune cells that have a possible role in this disease, they are also NK cells; indeed, their depletion exacerbates the disease in EAE (Chanvillard et al. 2013). Mast cells in the meninges contribute to the early development of EAE in rodent model (Sayed et al. 2010) and accumulate in plaque (Olsson 1974). Lastly, neutrophils of MS patients display a pro-inflammatory phenotype and infiltrate the CNS in the early stages of the disease (Hernandez-Pedro et al. 2013; Naegele et al. 2012; Hertwig et al. 2016) and seems to contribute, through the production of reactive oxygen species, at least at the brain level to the inflammatory response associated with the severity of symptoms (van Horssen et al. 2011; Steinbach et al. 2013).

Rheumatoid Arthritis

RA is an autoimmune disease in which the main characteristic is the irreversible joint destruction associated with progressive disability (McInnes and Schett 2011). It can occur at any age, but is most common between 40 and 60 years and the frequency is higher in women than men (Heidari 2011). Innate immunity is critical in the pathogenesis of RA. Macrophages infiltrating in the synovial tissues have a pivotal role and at present, the currently most widely used therapy includes methotrexate and proinflammatory cytokine inhibitors that act decreasing the production and/or the activity of cytokines such as TNF- α and IL-1, produced primarily by macrophages (Arend 2001). As in tumors, even in RA, macrophages display a pro-inflammatory phenotype, with reduced expression of pro-apoptotic genes and increased production of pro-inflammatory mediators, like IL-1 β (Gierut et al. 2010). Both in peripheral blood and in synovial fluids of RA patients, in comparison to healthy control, it was identified a little but significantly increased number of DC (Gierut et al. 2010), acting as antigen presenting cells and contributing to disease progression (Lutzky et al. 2007). Neutrophils, as well as NK, are prevalently found in synovial fluid of RA patients (Falgarone et al. 2005). They participate to the disruption of

joint (Kaplan 2013) and, releasing NET and producing pro-inflammatory cytokines, contribute to the development of the pathology, (Wright et al. 2014). The cross-talk with other immune cells leads to the release of cytokines, among which, TNF- α has the pivotal role in the onset of RA and also in the NK-dependent DC maturation (Shegarfi et al. 2012). On the contrary, NK cells can act as immune regulator against activated T cells and macrophages through their cytotoxic effects (Ahern and Brennan 2011; Arend 2001).

The dopaminergic system has a strong impact on RA (Pacheco et al. 2014) as suggested by the increased expression of DR on synovial fibroblasts of patients with RA (Capellino et al. 2014), that also present DA transporter, and tyrosine hydroxylase (Capellino et al. 2010). In a RA mouse model, Nakano and colleagues showed that DA released by DC induces the IL-6-dependent production of IL-17 by T cell that leads to the differentiation of Th₁₇ lymphocytes resulting in exacerbated cartilage destruction, and this effect is prevented by the D₁-like DR antagonist SCH-23390 (Nakano et al. 2011; Nakashioya et al. 2011).

Haloperidol, a D₂-like DR antagonist, showed an anti-RA effect, mitigating the effects due to oxidative stress in adult female albino rats (Fahmy Wahba et al. 2015) while the DR agonist cabergoline, reduced the levels of prolactin in ten female rats with active RA and contribute to the ameliorating of disease (Mobini et al. 2011). Despite the established role of innate immunity in RA, no studies so far evaluated the relationship between dopaminergic pathways and innate immune cells in the specific context of RA. The observations by Capellino et al. (2014) showing that elevated expression of DR in synovial fibroblasts of patients with RA is associated with an anti-inflammatory effect may suggest that dopaminergic agents lead to a reduction of inflammation, therefore indicating DR on immune cells as therapeutic targets even in RA.

Amyotrophic Lateral Sclerosis

ALS, also known as Lou Gehrig's disease and motor neuron disease, is a neurodegenerative disorder due to a progressive loss of neurons which control the voluntary muscles, characterized by weakness, muscle wasting, fasciculations, and increased reflexes. The disease is manifested by age 60, or earlier in cases of heredity. 90% of the cases are sporadic, with uncertain etiology, while 10% has a family history with mutations in several genes, among which superoxide dismutase-1 is the best characterized (Zhao et al. 2013b).

In 1993, Takahashi and colleagues hypothesized that sporadic ALS and idiopathic Parkinson's disease share the same pathogenesis, as evidenced by a progressive fall in 6-fluorodopa uptake during time (Takahashi et al. 1993). Some years later, through single photon emission computed tomography techniques, a deficit in the nigrostriatal dopaminergic pathway in a subset of patients with sporadic ALS was

demonstrated (Borasio et al. 1998). This evidence is corroborated by the low levels of homovanillic acid, the major catabolite of DA, in the cerebrospinal fluid of ALS patients (Mendell et al. 1971). Moreover, in *in vivo* experiments it was demonstrated a decreased DR D₂ binding in the striatum of ALS patients (Vogels et al. 2000). Indeed, the treatment with bromocriptine, a DR D₂ agonist, acts as neuroprotective agent and improves the motor function and slows the progression of the disease (Nagata et al. 2016).

Several lines of evidence suggest a potential involvement of innate immunity in the pathogenesis of ALS (Moisse and Strong 2006; Gendelman and Mosley 2015; Malaspina et al. 2015). At the level of CNS, in *in vivo* models, microglia activation occurs and increases in parallel to the development of ALS. In fact, *in vitro* experiments activated microglia, as well as astrocytes, leads to motor neuron death producing pro-inflammatory cytokines (Moisse and Strong 2006; Phani et al. 2012). Additionally, in a mouse model of ALS, peripheral monocytes exert a protective role, improving the survival of motor neurons after the infiltration in the CNS due to the frank breaching of the blood brain barrier (Zondler et al. 2016). ALS itself leads to a change in the phenotype and functions of monocytes (Zondler et al. 2016). On the contrary, infiltrating monocytes/macrophages can exacerbate the neurodegeneration with the release of pro-inflammatory mediators (Zhao et al. 2013b). Finally, the contribution of innate immunity is sustained by the recent finding of Murdock and colleagues of 2016, who showed an increase in the percentage of neutrophils and a decrease of the the percentage of monocytes in ALS patients compared to controls, even if only monocyte levels correlate with the progression of the pathology (Murdock et al. 2016). No direct evidence for dysregulation of DR pathways in immune cells exists so far in ALS, however the expression and functional relevance of DR in cells deeply involved in the pathogenesis of the disease, such as monocytes/macrophages and neutrophils, suggests that dopaminergic agents might affect at least some key mechanisms involved in ALS.

Alzheimer's Disease

AD is a neurodegenerative disorder that slowly destroys memories and intellectual ability. The symptoms range from an initial loss of short term memory, up to problems with speech and inability to take care of themselves. The causes are mostly unknown, but genetic heritability, traumatic brain injury, hypertension and depression are important risk factors. At the level of the brain, the formation of plaques constituted by β -amyloid protein and the neurofibrillary tangles formed by τ protein, determines a loss of connection between neurons and neuron death themselves (Bakota et al. 2017).

The role of the dopaminergic system in AD is still debated. It was highlighted that in 30–40% of AD patients, the

degeneration of dopaminergic neurons is linked with a deterioration of cognitive tasks (Lopez et al. 1997; Nobili et al. 2017). In mouse model of AD, it was demonstrated that the dysregulation of dopaminergic system is implicated in the decline of memory and learning (Martorana and Koch 2014). Pizzolato and colleagues found that alterations of DR D2 at the level of striatum may participate in the extrapyramidal manifestations that occur in AD (Pizzolato et al. 1996). Recently, several evidences about the role exerted by neuroinflammation in the course of AD are emerging (Guillot-Sestier MV and Town 2013; VanItallie 2017). In the review of Heneka and colleagues it was highlighted that the chronicle deposition of amyloid aggregate in the brain, activate the microglia, which release cytokines and mediators, exacerbating the neurotoxicity (Heneka et al. 2015). However, it was shown that IL-10/STAT3 pathway, can block the innate immune recognition at the level of brain, as well as the the phagocytosis, reducing the neuroinflammation (Guillot-Sestier MV1 et al. 2015). More recently, a key role of dopaminergic pathway wa reported. As example, Nobili and coworkers (Nobili et al. 2017) report that alteration of dopaminergic system in the midbrain is commonly linked with cognitive impairment in AD patients.

Innate immunity may have a role in AD. Indeed, after the rupture of blood brain barrier, neutrophils can migrate into the brain and, in a mouse model of AD, by means of in vivo imaging techniques it was observed that they infiltrate the amyloid plaques (Baik et al. 2014). In transgenic models of AD, it was observed that neutrophils are present at the level of amyloid plaques, where they release NETs and IL-17 contributing to neuronal damage and blood brain barrier disruption. Indeed, in animal models, neutrophils depletion reduces the severity of AD progression (Zenaro et al. 2015). Peripheral monocytes of AD patient migrate into the brain to remove the aggregates of amyloid and Saresella and colleagues showed that monocytes of AD patients have an inflammatory phenotype and are involved in the activation of both innate and acquired immunity (Saresella et al. 2014).

It was reported that the frequency of NK cells of AD patients is not modified, but they are less active (Jadidi-Niaragh et al. 2012) while peripheral myeloid DC are decreased in patients with AD, compared to controls, and this correlates with the severity and progression of pathology (Ciaramella et al. 2016).

As in ALS, no investigation exists on the involvement of DR pathways in immune cells in AD, with the only exception of one small study showing that DR mRNA levels in circulating PBMC do not differ between healthy subjects and AD patients (Cosentino et al. 2009).

HIV

HIV is a virus that attacks the cells of immune system, primarily CD4+ T cells and macrophages. There are two main types: HIV-1, the most common type found in the worldwide; and

HIV-2, mainly found in Western Africa. Several lines of evidences suggest the participation of innate immunity in the early phases of HIV infections. Macrophages are the primary target for of HIV in the CNS. It was indeed postulated that the entry of HIV in the brain is tightly linked with blood derived macrophages, as suggested by the presence of the virus in the conventional sites of macrophages, like meninges and the perivascular areas (Nottet and Gendelman 1995). The viral reservoir at the level of the brain is a substantial problem because current therapies with antiretroviral drugs present a variable blood-brain barrier penetration. The possibility to use macrophages as carriers of antiretroviral agents ~~is~~ was tested in mice during HIV-1 encephalitis by the group of Gendelman who found that the administration of bone marrow macrophages loaded with nanoparticles prepared using indinavir (an antiretroviral agent) could reach brain areas reducing the replication of the virus (Dou et al. 2009).

DA exerts a very strong impact on the function of macrophages during HIV infection. In drug abusers, increased DA levels in plasma correlate with enhanced entry of HIV into macrophages (Carbone et al. 1989; Gaskill et al. 2014). This effect requires the activation of DR expressed on monocyte-derived-macrophages (Gaskill et al. 2009; Gaskill et al. 2012), and it is suppressed by the D₁-like/D₂-like DR antagonist flupenthixol (Gaskill et al. 2014). Similarly, CD14 + CD16+ monocytes express the mRNA of all five DR and all DR are functional, as shown by the up-regulation of Erk2. Moreover, treatment with DA, as well as with the D₁-like DR agonist SKF-38393, increased cell migration and transmigration across an in vitro BBB model (Coley et al. 2015). Both infected and non-infected monocytes can cross the BBB. Two other components of innate immunity should be mentioned because it seems to play a role in the progression of HIV, namely DC and NK cells (Altfeld and Gale 2015). During HIV infections, DC play a pivotal role as sentinels that alert other cells ~~by~~ through the secretion of a series of cytokines, even if evidences exists about their contribute to HIV infection and progression (Manches et al. 2014). IFN- α -producing DC activate T cells and exert themselves an antiviral effect (Borrow and Bhardwaj 2008). However, although there are some signs of a possible modulation of dopaminergic system on these cells, such as the membrane expression of all the DR (Gaiazzi et al. 2016b), it is still unclear whether treatment with dopaminergic agents may alter some behaviors that may be useful in the course of the disease. Epidemiologic data strongly support also the role of NK cells in the antiviral control through the activation of killer immunoglobulin-like receptors (KIRs) (Carrington and Alter 2012).

Once in the brain, HIV disrupts central dopaminergic pathway also by acting on the dopamine transporter (DAT). By means of a computational model, a two amino acids mutation in DAT results in attenuation of the damage induced by HIV-1 protein transactivator of transcription (tat) (Midde et al. 2015).

Tat is a regulatory protein essential for the replication of the virus; mutant tat could inhibit the activity of HIV reverse transcriptase (Lin et al. 2015). Tat is also able to enhance Parkinson's-like behavior in the rats (Liu et al. 2014).

Septic Shock

Septic shock is a dangerous medical circumstance resulting from the aggravation of sepsis, a condition due to severe infection, leading to an abnormal distribution of the blood flow in the tissues (Singer et al. 2016). The treatment involves the use of antibiotics, the recovery of the fluids and the use of vasopressors, like dopamine and norepinephrine.

DA together with other inotropes is the first vasopressor used in the case of sepsis or septic shock that occurs during an overwhelming immune response to bacterial infections that trigger an inflammatory response throughout the body (Zhang and Chen 2016). The treatment with DA results in hemodynamic effects, like increase in blood pressure and flow and vasodilatation (McDonald et al. 1964) and endogenous DA itself increases under inflammatory conditions (Beck et al. 2004).

The DR-mediated effects on immune cells during sepsis are different. In neutrophils, there is a suppression of the respiratory burst, migration and TNF- α production, and an increase of apoptosis (Beck et al. 2004). The inhibition in cytokine production following treatment with DA was also shown in macrophages (Tarazona et al. 1995). Interestingly, Torres-Rosas et al. (2014), observed that the electroacupuncture in the sciatic nerve of mice increased the production of DA in the adrenal medulla. DA, acting on DR D₁, was in turn able to reduce the levels of cytokines and the systemic inflammation in the peripheral blood of mice, thus preventing the development of polymicrobial peritonitis (Torres-Rosas et al. 2014). DA is also able to modulate the secretion of several hormones during sepsis, for example prolactin (Bernton et al. 1988; Zhu et al. 1996, 1997). During sepsis, prolactin is decreased and this could be correlated with an impairment of the immune system leading to a susceptibility to infection (Beck et al. 2004).

However, there are some studies showing that norepinephrine is better than DA in the treatment of septic shock as it has fewer side effects (Sandifer and Jones 2012; Vasu et al. 2012). In particular, DA, in comparison to norepinephrine, was associated with increased arrhythmic events and mortality (De Backer et al. 2010, 2012; Martin et al. 1993; Hollenberg 2007; Xu and Peter 2011; Shenoy et al. 2011; Ventura et al. 2015; Avni et al. 2015).

From a general point of view, during infections the dopaminergic system undergoes profound changes. For instance, infection with *Toxoplasma gondii* induces significant changes in infected human and animal's behavior (Flegr 2007, 2013; Webster 2007; Vyas 2015), which at least in animals can be blocked by treatment with dopaminergic antagonists (Martin et al. 2015). Moreover, *Toxoplasma gondii* possess TH, the

rate-limiting enzyme in the synthesis of DA, and cells encysted with parasite may contain high levels of DA (McConkey et al. 2013).

Interestingly, it has also been suggested that DA, as well as noradrenaline, may alter bacterial internalization in Peyer's patches by acting on receptors situated on the intestinal epithelial cells (Brown and Price 2008; Green and Brown 2016).

Conclusions and Perspectives

Despite the extensive knowledge available on the role of dopaminergic pathways in the adaptive branch of the immune system (Basu and Dasgupta 2000; Sarkar et al. 2010; Levite 2012), comparatively little is known about dopaminergic modulation of innate immunity. Nonetheless, available evidence clearly points to a prominent role of dopaminergic mechanisms in the functional modulation of key innate immune cells such as neutrophils, monocytes/macrophages, NK cells, and dendritic cells. Much work remains however to be done and future studies should focus in particular upon:

- The pattern of expression and responsiveness of DR in relation to the functional conditions of the cells. DR exist in five molecular subtypes which can be divided into two main groups (D₁-like and D₂-like), and it has been shown that for instance in CD4⁺ T cells they undergo extensive modifications upon cell activation (Kustrimovic et al. 2014). It is conceivable that similar events occur also in innate immune cells, e.g. in neutrophils during activation, in the differentiation of monocytes towards macrophages, in dendritic cells during the process of antigen presentation, etc.;
- The specific role of distinct DR in the control of defined functional responses in the various cells. In general, in human T cells D₁-like DR are inhibitory while D₂-like DR result in the stimulation of various functions (Cosentino and Marino 2013). What about innate immune cells?
- DA, as well as noradrenaline and adrenaline, can be produced and used as transmitter by immune cells themselves (Cosentino and Marino 2013; Marino and Cosentino 2013; Scanzano and Cosentino 2015). Are innate immune cells able to produce endogenous DA? And is endogenous DA involved in the autocrine/paracrine regulation of immune cells themselves, like it has been shown in human T cells (Cosentino et al. 2007), and/or in the interplay between immune cells and other cells and tissues?
- In addition, it is increasingly clear that innate immune cells can be divided into distinct subsets with relevant functional differences, e.g. conventional and nonconventional (proinflammatory) monocytes (Ziegler-Heitbrock 2015), plasmacytoid and myeloid dendritic cells (Kushwah and Hu 2011). It is likely that DR expression and function may be different in the various subsets;

- Last but not least, it is clear that DR expression and responsiveness as well as DA production in the adaptive immune system undergo extensive changes during disease states, a phenomenon which has been extensively characterized in multiple sclerosis (Cosentino and Marino 2013; Marino and Cosentino 2016), and to some extent also in rheumatoid arthritis (Capellino et al. 2010; Capellino et al. 2014) and in Parkinson's disease (Kustrimovic et al. 2016). Investigation of possible changes of dopaminergic pathways during disease states is mandatory also in the innate immune system.

From a general point of view, the limited knowledge about the contribution of innate immunity into several major human diseases, such as autoimmunity, and neurodegeneration, may limit the possibility to assess the clinical relevance of available information concerning dopaminergic modulation of innate immune cells. Nonetheless, the established role of dopaminergic mechanisms in human disease such as multiple sclerosis (Cosentino and Marino 2013; Marino and Cosentino 2016), rheumatoid arthritis (Capellino et al. 2010; Nakano et al. 2011), Parkinson's disease (González et al. 2013; Kustrimovic et al. 2016) strongly support the opportunity to better characterize dopaminergic modulation of innate immunity as a way to identify novel therapeutic approaches. The pathogenetic and therapeutic implications of dopaminergic modulation of HIV infectivity in human monocytes (Gaskill et al. 2013, 2014; Williams et al. 2014) is a prominent example in this regard.

Innate immunity is able to influence the activity and response of cells of acquired immunity, and some evidence exists that DA may act as a transmitter between innate and adaptive immune cells, e.g. in particular regarding the Th1/Th2 balance as described by Nakano and colleagues who report that dopamine present in DC induces a shift vs Th2 differentiation while on the contrary dopamine depletion induce the Th1 differentiation (Nakano et al. 2009). Additionally, D1-like antagonist reduce the Th17-induced response and ovalbumin antigen-induced activation of neutrophils in a mouse model of airway inflammation (Nakagome et al. 2011).

The role of DA in the cross-talk between innate and adaptive immunity, including antigen processing and presentation and the triggering of different immune responses, is another area of great interest which awaits thorough investigation.

As a final recommendation, future studies should not only address the direct effects of DA but also of the several dopaminergic agonists with peculiar DR selectivity profiles which are currently used in therapeutics for non-immune indications (Table 1). Besides providing useful information about the specific contribution of the various DR in different cells and tissues, such studies could strengthen the rational basis for the development of clinical trials of these drugs for immune-mediated disease. Such drugs have usually favorable therapeutic index, and also in view of their established use they

might be developed at a relatively low cost, which significant benefit for patients as well as for the healthcare systems (Cosentino et al. 2017).

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing financial interests.

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