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The role of dopamine receptors in lymphocytes and their changes in schizophrenia

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ABSTRACT

Dopamine and its 5 receptors, which are grouped into two families (D1-like and D2-like), modulate functions at a systemic level in both the central nervous system and periphery. The central nervous system and the immune system are the main adaptive systems, which participate in a continuous and functional crosstalk to guarantee homeostasis. On binding to its 5 dopamine receptors, dopamine acts as a co-regulator of the immune system, contributing to the interaction of the central nervous system and inflammatory events and as a source of communication between the different immune cells. Dopaminergic perturbations in the central nervous system are observed in several neurological and psychiatric disorders. Schizophrenia is one of the most common mental disorders with a poorly understood pathoaetiology that includes genetic and environmental components that promote alterations in the dopaminergic system. Interestingly, abnormalities in dopamine receptors expression in lymphocytes of schizophrenia patients have been reported, often significantly correlating with the severity of the psychotic illness. Here, we review the current literature regarding the dopaminergic system in human lymphocytes and its alterations in schizophrenia.

1. Introduction

Dopamine (DA) is part of the catecholamine family and was first synthesized in 1910 by George Barger and James Ewens (Barger and Dale, 1910; Mannich et al., 1910). Later, DA was found to be an important member of the group of neurotransmitters called biogenic amines and have primary functions and a remarkable distribution in the brain and as well as the rest of the body (Roe, 1999). The effects of DA are mediated by the union of the primary endogenous ligand with the DA receptors (DRs).

There are 5 major subtypes of DRs that belong to a superfamily of metabotropic G-protein-coupled receptors of seven A-class transmembrane domains (Harmar et al., 2009), divided into two families according to their pharmacological profile. The D1-like receptor subtypes (D1R and D5R) are stimulatory receptors coupled to the Gαs-protein and the D2-like receptor subtypes (D2R, D3R and D4R) are inhibitory receptors coupled to the Gαi/o-protein, depending on their ability to subsequently activate the enzyme adenylyl cyclase, increasing or not the intracellular concentration of the secondary messenger cyclic adenosine monophosphate (cAMP), respectively (Kebabian, 1978; Beaulieu et al., 2015; Spano et al., 1978). Interestingly, DRs can form heterodimers leading to a particularly organized, varying combinatorial possibilities at a higher level, which gives this family of receptors very diverse pharmacological and functional properties (Beaulieu et al., 2015).

DA is best known for its role as a neurotransmitter, participating in a wide variety of functions in the brain including: control of movement, behaviour, motivation, cognition, and reward. Dopaminergic neurons primarily synthesize DA and are located within the *substantia nigra pars*

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compacta and ventral tegmental area in the mesencephalon. Dopaminergic projections form a large network of connections through 3 pathways that begin in the midbrain: the nigrostriatal pathway which innervates dorsal areas, the mesolimbic which projects to ventral areas, while prefrontal cortical areas are reached via mesocortical pathway projections (Kandel et al., 2000; Cave and Baker, 2009). In addition, there is a fourth pathway called tuberoinfundibular that connects the hypothalamus to the anterior pituitary to inhibit prolactin secretion (Porter et al., 1990).

Given that DA cannot cross the blood-brain-barrier, the existence of DA in the bloodstream suggests the presence of dopaminergic components that modulate functions at a systemic level; therefore, its effects are not limited to the central nervous system (CNS) and the signalling in the neuronal dopaminergic system should be independent from that of the peripheral systems (Rubí and Maechler, 2010; Arreola et al., 2016). Plasma DA levels are regulated primarily by their release from sympathetic nerve fibbers, which innervate the secondary lymphoid tissues that store high concentrations of DA. Under physiological conditions, plasma DA levels are estimated to be $\sim 10^{-10}$ M – 10^{-11} M. The 5 DRs are co-expressed at different quantities and in numerous combinations in the CNS and peripheral tissues (Kirillova et al., 2008). Both primate and rodent brains express a higher density of D1-like than D2-like subtypes in healthy conditions (Weinstein et al., 2017).

The CNS and the immune system are the main adaptive systems, which participate in a continuous and functional crosstalk to guarantee homeostasis (Arreola et al., 2016; Franco et al., 2007; Basu and Dasgupta, 2000). By binding to its receptors, DA acts as a co-regulator of the immune system, contributing to the interaction between the immune cells and the CNS and as a source of communication between the different immune cells (Arreola et al., 2016; Franco et al., 2007; Basu and Dasgupta, 2000; Sarkar et al., 2010; Levite and Levite, 2012; Rodrigues-Amorim et al., 2018; Stahl, 2017a).

Dopaminergic perturbations in the CNS are observed in several neurological and psychiatric disorders (Stahl, 2017a; Grace, 2016). Schizophrenia (SCZ) is one of the most common mental disorders that affects about one per cent of the world's population. SCZ is a chronic and frequently disabling syndrome with a poorly understood pathoaetiology, that includes genetic and environmental components promoting alterations in the dopaminergic system (Slifstein et al., 2015; Marder and Cannon, 2019). Interestingly, abnormalities in the expression of DRs in lymphocytes (LYM) of schizophrenic patients have been reported, which often significantly correlate with psychotic illness severity (Liu et al., 2013). Here, we review the current literature pertaining to the dopaminergic system in human LYM and how it is altered in one of the main psychiatric diseases, SCZ. Information was gathered by searching the PubMed Services database using the following keywords: dopamine, dopamine receptors, lymphocytes, schizophrenia. We have also included relevant articles referenced in the bibliographies from all the articles searched as well as historically remarkable or conceptually related articles.

2. Dopamine receptors in lymphocytes

LYM are the principal cells of the adaptive immune system that differentiate into many subpopulations with a wide variety of functions. These cells can modulate, regulate and coordinate the activities of other immune cell populations through cytokine secretion, and at the same time, can respond to circulatory levels of cytokines, hormones, and neurotransmitters (Levite and Levite, 2012; Rodrigues-Amorim et al., 2018; Bergquist et al., 1994). The effects by DA-mediated activation of the different DRs on diverse immune cell types show different sensitivities to DA, but the binding profiles of DA on T cells are similar to those in neuronal membranes, suggesting the receptors act similarly to those found in neurons (Matt and Gaskill, 2020).

The idea that neurotransmitters could serve as immunomodulators came with the finding that their discharge and diffusion from nervous tissue could give rise to signalling through LYM membrane receptors and modulation of immune function (Franco et al., 2007). In the late 20th century, several studies showed that LYM have the metabolic capacity to synthesize DA and its metabolites, although at a very low concentration of $\sim 10^{-18}$ mol/cell, and the DRs are present as functional receptors on the cell surface, that bind and respond to DA and its analogues (Bergquist et al., 1994). The main source of DA could be within the immune system itself, as the immune cells can capture circulating plasma DA through active transport using DAT, a Na +/Cl-dependent DA transporter (Faraj et al., 1994; Amenta et al., 2001; Marino et al., 1999; Pacheco et al., 2009), and release it in physiological and pathological conditions, acting as an autocrine/paracrine modulator in immune cells and neighbouring cells (Arreola et al., 2016; Basu and Dasgupta, 2000; Liu et al., 2013; Pacheco et al., 2009; Faraj et al., 1991). LYM regulate their DA concentration very finely, holding it at a basal level of 1.6×10^{-18} mol/cell, through a balance between the internal, its synthesis and transported DA.

Searching for DA receptors on LYM has been a challenging mission. Using different laboratory techniques, such as: flow cytometry (Kustrimovic et al., 2014; McKenna et al., 2002; Levite, 2016), RT-PCR and qRT-PCR (Kirillova et al., 2008; Bondy et al., 1996; Arce-Sillas et al., 2019; Ostadali et al., 2004), radio ligand binding assays (Kirillova et al., 2008; Amenta et al., 1999; Santambrogio et al., 1993; Ricci et al., 1997) and western blot (Franco et al., 2007), it has been observed that all DRs are differentially expressed in almost all LYM lineages. Although, in most reports only some types of immune cells and some types of DRs were studied.

DA can affect most, if not all immune cells and the expression of all DRs depends on the state of cellular activation and concentration and the time of exposure to DA (Sarkar et al., 2010; Levite and Levite, 2012; Kustrimovic et al., 2014). DRs mRNA and protein levels vary among immune cell subpopulations: T LYM and monocytes have the lowest DR expression, neutrophils and eosinophils a moderate expression, while B LYM and NK cells have the highest and most consistent levels (McKenna et al., 2002; Levite, 2016; Arce-Sillas et al., 2019). Work by McKenna et al. tells that some immune cells have higher levels of DRs than others, where the expression of D3R and D5R is stable and always detected in LYM, while the expression of D2R and D4R is more variable, but D1R expression was not revealed (McKenna et al., 2002). 5 years later, D1R expression was demonstrated in effector and regulatory T cells (Cosentino et al., 2007; Nakano et al., 2008).

In a very interesting study (Kirillova et al., 2008), the expression levels of DRs in the brain were compared with those of peripheral blood mononuclear cells (PBMCs), and it was revealed that the expression levels of mRNA of D3R and D4R in the PBMCs were equivalent with those in the brain for these receptors, and were significantly lower for mRNA of DR2 and DR5. However, the relative expression of DRs in LYM was not parallel to that of the brain.

In summary, it can be confirmed that all DRs are expressed on the LYM membrane. However, more detailed information is required on the expression patterns of DR in immune cells in healthy conditions and in pathologies, regarding the differences between cell subsets and the relationship to the functional status of cells.

3. Effects of dopamine on lymphocytes

It has been proposed that DA could be referred to as a 'neuro-immune-transmitter', because in the last 2 decades direct and potent DA-induced functions in most immune cells have been discovered, many of them of high importance (Levite and Levite, 2012). The most notable immuno-modulatory functions of DA are carried out during the immune response, where DA selectively regulates the activation of different phenotypes of LYM and the communication between immune cells (Kustrimovic et al., 2014; Nakano et al., 2008; Kipnis et al., 2004). DA has been observed to influence LYM functions acting in a variety of important processes, like cytokine secretion, cell adhesion, chemotaxis, and cytotoxicity (Arreola et al., 2016; Arce-Sillas et al., 2019; Levite

et al., 2001; Cosentino et al., 2004; Besser et al., 2005; Watanabe et al., 2006; Nakano et al., 2009).

The overall effects of DA on LYM depends on the context in accordance to the following parameters (Levite and Levite, 2012; Vidal and Pacheco, 2020):

A. Concentrations of DA: different DA concentrations often induce different and even opposite effects in immune cells. At a normal concentration of ~10^{-8} M (0.1 nM), DA usually produces specific and physiological effects, but when this concentration is at a very high level of ~ 10^{-4}–10^{-2} M (0.1–10 mM), then nonspecific and even toxic effects are induced on oxidative metabolism in immune cells, often evoking apoptosis (Matt and Gaskill, 2020; Cosentino et al., 2004, 2007). Monocyte-derived dendritic cells store DA in secretary vesicles, and antigen-specific interaction with naïve $CD4^+$ T cells induces the release of this DA (Nakano et al., 2009).
B. The activation state of the immune cell: DA frequently activates naïve immune cells, especially T cells, but DR activation by DA or other stimuli inhibits activated immune cells (Levite and Levite, 2012; Mignini et al., 2013).
C. The specific type of the immune cell: DA on its own activates naïve normal human T cells, and drives them to function (Levite et al., 2001), while $CD8^+$ T cells seem to be more reactive to DA-mediated inhibition than $CD4^+$ T cells (Saha et al., 2001).
D. The specific activated DR as well as the DRs that are expressed on the same immune cells membrane: Different immune cells have different levels of D1R-D5R subtypes, D1-like receptors are highly expressed in both naïve and memory T cells, while the D2-like receptors are expressed mainly in memory T cells and only marginally in naïve cells (Nakano et al., 2008; Mignini et al., 2013).

3.1. DA on D1-like receptors

In human LYM, DA on D1-like receptors (Fig. 1A) decreases oxidative metabolism and apoptosis (Cosentino et al., 2004), activates the selective secretion of IL-10 and TNFα, and facilitates NK cells (Besser et al., 2005; Zhao et al., 2013). As well, D1R-like antagonists inhibit Th17 production, increasing IFNγ (Nakano et al., 2008).

D1R are expressed in stimulated T LYM and are related to the negative regulation of the immune response (Basu et al., 2010) by inhibiting the synthesis of DA (Ferrari et al., 2004). Specifically, in $CD4^+$ and $CD8^+$ cells, DA activation via D1R-mediated stimulation of intracellular cAMP inhibits proliferation and cytotoxicity, resulting in a polarization towards a Th2 phenotype of naïve $CD4^+$ (Nakano et al., 2009; Saha et al., 2001). Regulatory T cells ($CD4^+CD25^+$ Tregs) express significantly more D1R than naïve effector T cells (Teffs), and their activation impairs the generation and function of Teffs (Cosentino et al., 2007; Besser et al., 2005; Watanabe et al., 2006; Saha et al., 2001), attenuates the negative feedback on suppressive activity and trafficking of Tregs (Kipnis et al., 2004), and inhibits activated T cells (Cosentino et al., 2007). Also, D1R activation inhibits intracellular DA production in PBMCs which promotes cell survival through reduction of activation-induced apoptosis (Ferrari et al., 2004).

The signalling of D5R in T cells exerts a pro-inflammatory effect (Pacheco, 2017). Specifically, D5R activation in naïve $CD4^+$ cells is associated with an exacerbated proliferation in response to T cell activation (Franz et al., 2015), in Teffs with favouring the acquisition of the Th17 inflammatory phenotype, and in Tregs with increasing the potency of their suppressive activity (Osorio-Barrios et al., 2018).

3.2. DA on D2-like receptors

In contrast, most of the immunostimulatory DA effects on LYM depend on stimulation of D2-like receptors (Fig. 1B), including activation, proliferation, differentiation, and suppression of NK cells (Arreola et al., 2016; Franco et al., 2007; Watanabe et al., 2006; Zhao et al., 2013; Huang et al., 2016).

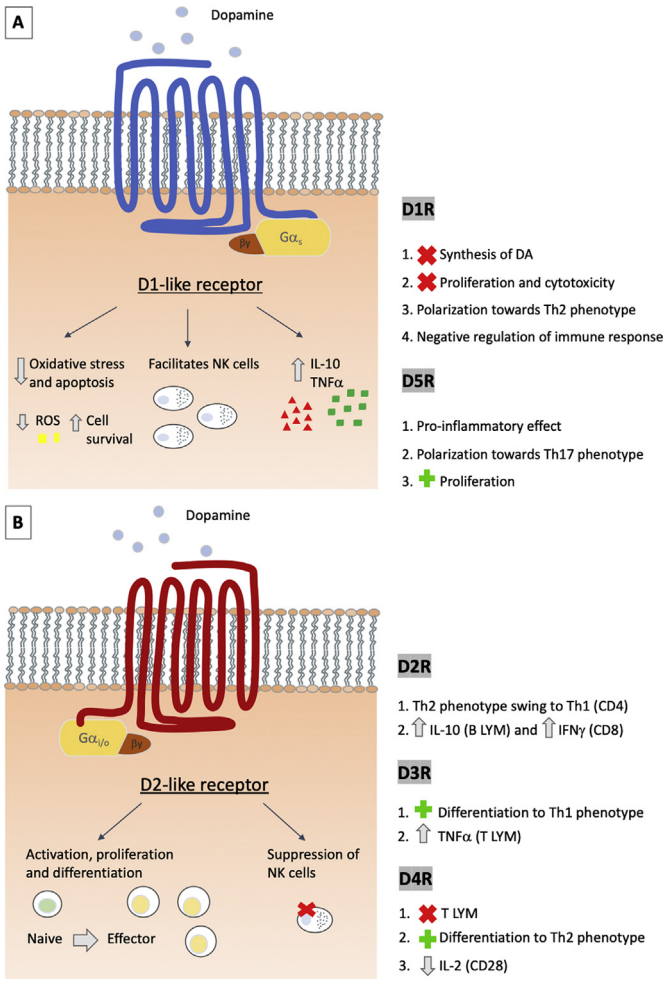

Fig. 1. Main functions of DA on LYM: **A.** D1-like receptors **B.** D2-like receptors. (Red cross = inhibition and green cross = enhancement).

In T LYM, the binding of DA to D2R and D3R produces an increase in trafficking dependent on integrins, resulting in a stimulation of chemotaxis migration, selective adhesion to extracellular matrix, and homing of activated $CD8^+$ cytotoxic T cells in the periphery (Levite et al., 2001; Watanabe et al., 2006). They are also associated with an immune regulatory response (Nakano et al., 2009), activating the production of inflammatory TNFα by D3R stimulation and anti-inflammatory IL-10 by D2R stimulation in T and B LYM, respectively (Besser et al., 2005). On the contrary, it seems that D4R signalling induces T cell inactivity and is not expressed in $CD19^+$ B LYM (Watanabe et al., 2006), where D4R agonists down regulate the proliferation and IL-2 secretion of activated T cells ($CD3^+CD28^+$) (Sarkar et al., 2006).

Stimulation of D2R in activated $CD4^+$ T cells cause a Th2 to Th1 swing, and trigger IFNγ production in activated $CD8^+$ T cells (Ilani et al., 2004). D3R signalling in T cells enhances their activation, favouring differentiation towards Th1 phenotype and mutually buffering the acquisition of the Th2 phenotype (Franz et al., 2015; González et al., 2013; Contreras et al., 2016). A recent study revealed that D4R signalling on T cells favours Th2 differentiation (Huang et al., 2016; Wang et al., 2019).

Taken together, these findings indicate that LYM could undergo a complex dopaminergic regulation. It is interesting to note that these immune functions in turn can affect dopaminergic signalling both centrally and peripherally, and dopaminergic neurotransmission is

important to immunoregulation in physiological and pathological conditions. Altered levels of DRs expressed in immune cells, and/or changed response of immune cells to DA, may play a role in some neurological and psychiatric diseases (Huang et al., 2016). It could be thought that, if there are alterations in the neuronal dopaminergic system under pathological conditions, there would also be alterations in the rest of the peripheral dopaminergic systems such as the ones that influences immune cells.

4. Changes in the dopaminergic system of lymphocytes associated with schizophrenia

SCZ is a heterogeneous chronic psychiatric syndrome characterized in its most common form by psychotic or positive symptoms (hallucinations, paranoid delusions and disorganized speech), by negative symptoms (decreased motivation and expressiveness with impaired social interaction), and by cognitive deficits involving executive functions, memory and speed of mental processing. SCZ often manifests during late adolescence or early adulthood, and the prevalence of this disorder reaches almost 1% of the world's population (with an annual incidence that ranges between 3.89 and 4.03 per 1000 subjects) (Moreno-Küstner et al., 2018) and is one of the top 10 global causes of disability with 80% heritability in population (Fleischhacker et al., 2014).

Its aetiology is not yet clear and includes genetic, neurobiological and environmental components that promote alterations in dopaminergic signalling. The classical DA hypothesis postulates an imbalance in dopaminergic transmission with hyperactive zones, such as the mesolimbic areas, striatum and hippocampus, and hypoactive, deficient signalling in the prefrontal cortex (PFC) of SCZ patients (Weinstein et al., 2017; Slifstein et al., 2015; Weinberger, 1987; Howes and Kapur, 2009). Interestingly, this paradigm indicates that D2R hyperactivity subcortically contributes to positive symptoms and D1R hypofunctionality in the cortex is involved in the negative symptoms (Stahl, 2017a; Howes and Kapur, 2009; Abi-Dargham and Moore, 2003; Laruelle et al., 1999; Abi-Dargham et al., 2000). D3R in the midbrain may also play a role in the modulation of negative symptoms, mood and cognitive deficits of the disease enhancing DA neurotransmission to PFC and nucleus accumbens (Stahl, 2017a; Sokoloff and Le Foll, 2017; Neill et al., 2016; Millan et al., 2012). Although the introduction of antipsychotic medications more than 60 years ago has substantially improved the treatment of the positive symptoms of SCZ, the disease still causes considerable morbidity and mortality (Saha et al., 2007).

The current diagnosis of SCZ and the establishment of a therapeutic approach are mostly based on clinical questionnaires that confirm that patients meet established criteria for the disorder, such as the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) (American Psychiatric Association, 2013). The clinical response is often characterized for recurrent relapses for those patients who discontinue medication or have changes in the adherence, which are associated with adverse outcomes, including symptoms resistant to treatment, cognitive decline, and chronic functional disability (Marder and Cannon, 2019; Emsley et al., 2013).

The DRs are the most common targets of antipsychotics, such as haloperidol, risperidone or aripiprazole, among others, that modulate DA neurotransmission by receptor occupancy (Slifstein et al., 2015; Marder and Cannon, 2019). However, antipsychotics are not clinically effective at alleviating all symptoms associated with SCZ and may exacerbate cortical-related symptoms, such as negative symptoms and cognitive impairment, including extrapyramidal motor syndromes (Li et al., 2016). There is a new classification of drugs for psychosis according to which DRs they bind, which have functional differences with potential clinical implications: those that preferentially bind D2R (most of them), D3R and D1R (Stahl, 2017b). To date, an altered expression or signalling of neurotransmitter receptors is observed in immune cells during psychiatric disorders and, consequently, these cells also markedly respond to antipsychotics (Matt and Gaskill, 2020; Faraj et al., 1991; Huang et al., 2016). Taken together, these findings support the involvement of active cross-talk between the dopaminergic and immune systems in the pathophysiology of SCZ (Vidal and Pacheco, 2020).

Besides alterations in the dopaminergic system in the CNS, it has been suggested that the DRs found on LYM may reflect the status of homologous brain DRs (Tomasik et al., 2016; Buttarelli et al., 2011; Rollins et al., 2010). Various aspects of the dopaminergic system have been investigated in peripheral blood samples from patients with SCZ to find reliable peripheral biomarkers of diagnosis and pathological severity (Rodrigues-Amorim et al., 2017), including analysis of the expression of DRs in peripheral blood lymphocytes (PBLs). Interestingly, the expression levels of DRs in LYM of SCZ patients were often significantly different from those in LYM of healthy individuals, but the results have been conflicting (Table 1).

4.1. D1-like receptors

D1R expression in LYM has always been highly controversial. No expression was detected in LYM from patients with SCZ by two groups of researchers (Boneberg et al., 2006; Fernandez-Egea et al., 2016). However, in another article D1R was expressed in 100% of the LYM of healthy controls and treated and drug-naïve SCZ patients, but, statistically significant differences were not found between SCZ patients and controls (Ahmadian et al., 2014).

On the other hand, in drug-free SCZ patients that did not take antipsychotics for more than 3 months, D5R mRNA expression in PBLs are increased compared to that of drug-medicated SCZ (Kwak et al., 2001). Little is known about the D5R because, according to some authors, RT-PCR is not possible since it has at least two transcribed pseudogenes, which exhibit high nucleotide sequence homology (approximately 95%) to the functional gene (Takahashi et al., 1992), occasioning a strong limitation in primer design possibilities that do not amplify genomic DNA (Boneberg et al., 2006).

Nevertheless, some reports suggest that the D1R may be related to the negative symptoms (Davidson et al., 1990; Stenkrona et al., 2019) and the fact that the D5R in the PFC is down-regulated by antipsychotics in an animal experiment may suggest that the D5R is also related to SCZ (Lidow et al., 1997).

4.2. D2-like receptors

4.2.1. D2R

Regarding the characterization of the expression patterns of D2R (Table 2), according to one article they are not expressed on leukocytes (Boneberg et al., 2006), but in a study by Ahmadian et al., expression rated in LYM of healthy controls was 6.66%, in drug-free SCZ patients who had not taken antipsychotic drugs for more than 3 months 40% and in patients who had been taking antipsychotic drugs for more than 3 years 20% (Ahmadian et al., 2014). Though, statistical comparison between groups showed no significant differences (Ahmadian et al., 2014; Yao et al., 2008), as was found in T LYM among healthy controls and patients with early psychosis and SCZ/schizophreniform disorder (Cui et al., 2015). On the other hand, another article showed for the first time that the D2R gene in the PBLs was significantly overexpressed in drug-naïve/drug-free SCZ patients when compared to healthy controls (Zvara et al., 2005). Since neither the affected nor the non-affected individuals were under antipsychotic treatment or other medication, elevated D2R mRNA levels here reflected the disorder itself rather than the effect of medication (Zvara et al., 2005), as could also be seen in an assay where the specific binding of the DA antagonist 3H-spiperone was significantly increased in LYM from SCZ patients (Bondy et al., 1985).

By means of flow cytometry, increased percentages of $CD8^{+}D2R^{+}$ cells were observed in SCZ patients hospitalized over a 10-year period and receiving typical antipsychotic treatment, albeit this population revealed lower $CD4^{+}D2R^{+}$ cells in comparison to controls (Brito-Melo et al., 2012). These results suggest a cell specific alteration of the expression of D2R in the LYM of SCZ patients (Brito-Melo et al., 2012).

Table 1
Findings of DRs expression in LYM of patients with SCZ.

Reference	Findings
Bondy et al., 1985	Increased D2-like binding (of 3H-spiperone)
Kwak et al., 2001	Increased D3R mRNA (drug-free vs medicated and controls)
	No differences in D3R mRNA (drug-free vs drug-naïve)
	After taking antipsychotics, D3R peaked at 2nd week, which later at 8th decreased
	Increased D5R mRNA (drug-free vs medicated)
van der Weide et al., 2003	No differences in D3R mRNA
Ilani et al., 2004	Increased D3R mRNA in SCZ
	No differences in D4R mRNA
Vogel et al., 2004	Reduced D3R mRNA (drug-naïve vs controls)
Zvara et al., 2005	D2R mRNA over-expressed
Rodrigues et al., 2005	No differences in D3R and D4R protein levels
	Significant inverse correlation (BPRS hebephrenic dimension score vs D3R, D4R)
Boneberg et al., 2006	D1R and D2R are not express
	Increased D3R mRNA in T cells
	Decreased D4R mRNA in T cells
Yao et al., 2008	No differences in D2R mRNA
Kawano et al., 2011	No differences in D3R and D4R mRNA
	D3R mRNA inversely correlated with the total PANSS score
	D4R mRNA positively correlated with working memory scales
Urhan-Kucuk et al., 2011	No differences in D3R mRNA
	Significant differences in D3R mRNA (controls vs disorganized SCZ, disorganized SCZ vs paranoid SCZ)
Brito-Melo et al., 2012	Increased percentages of $CD8^+D2R^+$ cells
	Lower percentages of $CD4^+D2R^+$ cells
	Increased percentages of $CD4^+D4R^+$ and $CD8^+D4R^+$ cells
	BPRS and PANSS positively related to $CD8^+D2R^+$ cells
	AIMS positively related to $CD4^+D2R^+$ cells
	AIMS inversely related to $CD4^+D4R^+$ cells
Liu et al., 2013	No differences in D2R mRNA
	Significant relationship between D2R mRNA and positive symptom score of PANSS in acute SCZ patients
Ahmadian et al., 2014	D1R, D2R and D4R expressed in all groups but no differences in mRNA
	D3R expressed in all groups, increased mRNA in drug-free patients vs controls and significant differences between drug-naïve patients vs controls
Cui et al., 2015	No differences in D2R mRNA
	Significant positive correlation between D2R mRNA vs excited factor of PANSS in SCZ/schizophreniform patients
	Significant differences in D3R mRNA (controls vs psychotic and SCZ/schizophreniform patients)
Fernandez-Egea et al., 2016	Increased D3R mRNA in clozapine-treated SCZ patients
	No differences in D4R mRNA

Abbreviations: Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Abnormal Involuntary Movement Scale (AIMS).

Interestingly, a relationship between clinical symptoms and immunological parameters was also observed. The scores of BPRS and PANSS were positively related to $CD8^+D2R^+$ cells and the Abnormal Involuntary Movement Scale (AIMS) was positively related to $CD4^+D2R^+$ cells, in institutionalized chronic SCZ patients (Brito-Melo et al., 2012). These relationships are corroborated by other articles which show that there was a significant correlation between mRNA D2R levels in PBLs and the positive symptom score of PANSS in acute patients experiencing their first episode with an illness duration of less than 1.5 years (Liu et al., 2013), and that symptom severity was related to the excited factor of the PANSS in T LYM of patients with SCZ/schizophreniform disorder (Cui et al., 2015). In chronic SCZ patients, a significant relationship between D2R mRNA levels and positive symptom score of PANSS was not found (Liu et al., 2013).

This result can echo the "DA hyperfunction hypothesis'' of SCZ and the idea from psychopharmacology that mutual verification of antipsychotic drugs controls the positive symptoms of SCZ through their effects on D2R (Liu et al., 2013).

4.2.2. D3R

The D3R (Table 3) has been the most investigated of all 5 DRs in LYM of SCZ patients. Several studies have examined D3R mRNA levels in LYM in patients with SCZ, but the results are quite conflicting, demonstrating an increase (Ilani et al., 2004; Kwak et al., 2001; Vogel et al., 2004; Boneberg et al., 2006; Ahmadian et al., 2014; Fernandez-Egea et al., 2016), as well as a decrease (Vogel et al., 2004), or no differences (van der Weide et al., 2003; Zvara et al., 2005; Rodrigues et al., 2005; Kawano et al., 2011; Urhan-Kucuk et al., 2011). Thus, it is not clear whether D3R mRNA levels are altered in the PBLs of patients with SCZ, and many authors propose it as a biomarker candidate for diagnosing and follow-up of SCZ (Ilani et al., 2004; van der Weide et al., 2003; Ahmadian et al., 2014; Cui et al., 2015).

In general, it seems that D3R is influenced by antipsychotic treatment but not by the different substances taken, typical or atypical (Ilani et al., 2004; van der Weide et al., 2003; Zvara et al., 2005). The discrepancies observed may depend on the intake time, the necessary time to give a positive medication effect or a compensatory response of the receptor blockage due to the administration of antipsychotics, and considering mRNA expression levels of D3R in PBMCs are comparable to those in the brain (Kirillova et al., 2008).

There are significant differences between naïve patients with early psychosis and SCZ, who had never taken antipsychotic drugs, and healthy controls (Ahmadian et al., 2014; Cui et al., 2015), an increased in D3R expression being observed in drug-free patients who had not taken antipsychotic drugs for more than 3 months in comparison to controls (Ahmadian et al., 2014) and drug medicated patients for more than 3 years, whom were considered stable (Kwak et al., 2001). Interestingly, antipsychotics medication caused D3R expression to peak at the 2nd week, but decreased its expression later at the 8th week where it continued like this till after 1 year or even 3 years of treatment, becoming similar to those of healthy controls or at least not statistically different (Ilani et al., 2004; Kwak et al., 2001; van der Weide et al., 2003; Vogel et al., 2004; Kawano et al., 2011). This might be caused by down-regulation of D3R production by antipsychotic drug treatment when it reaches the desired effect.

In addition, D3R was detected in $CD4^+$ T cells and was found to be significantly increased in SCZ patients taking clozapine, which was correlated with a proportionally reduced frequency of Tregs, in which DR expression is abnormal in patients with treatment-resistant SCZ (Fernandez-Egea et al., 2016). In this group of patients, it could be thought

Table 2
Findings of D2R expression in LYM of patients with SCZ.

Reference	Study	n	Sample	Methodology	Clinical features	Findings
Bondy et al., 1985	Healthy controls	40	LYM	Receptor binding assay	ND	Increased D2-like binding (of 3H-spiperone)
	Unmedicated SCZ patients	27				
	Psychiatric control group	16				
Zvara et al., 2005	Healthy controls	10	PBLs	qRT-PCR	PANSS, CGIS, GAF,	D2R mRNA over-expressed
	Drug-free/Drug-naïve SCZ patients	13			Duration of illness, Medication	
Boneberg et al., 2006	Healthy controls	10	Leukocyte population	qRT-PCR	ND	D2R is not express
	SCZ patients	10	PBMCs			
Yao et al., 2008	Healthy controls	26	PBMCs	qRT-PCR	Duration of treatment	No differences in D2R mRNA
	First-hospitalized SCZ patients	30				
Brito-Melo et al., 2012	Healthy controls	20	LYM (CD4, CD8)	Flow-cytometry	CGIS, BPRS, PANSS, AIMS,	Increased percentages of $CD8^+D2R^+$ cells
	SCZ patients	40			Duration of illness and hospitalization, Dose of antipsychotic	Lower percentages of $CD4^+D2R^+$ cells
						BPRS and PANSS positively related to $CD8^+D2R^+$ cells
						AIMS positively related to $CD4^+D2R^+$ cells
Liu et al., 2013	Healthy controls	30	PBLs	qRT-PCR	PANSS, Duration of illness	No differences in D2R mRNA
	Acute SCZ patients	25				Significant relationship between D2R mRNA and positive symptom score of PANSS in acute SCZ patients
	Chronic SCZ patients	27				
Ahmadian et al., 2014	Healthy controls	20	PBLs	RT-PCR	ND	D2R expressed in all groups but no differences in mRNA
	Drug-naïve SCZ patients	5				
	Drug-free SCZ patients (» 3 months)	15				
	Drug-medicated SCZ patients (» 3 years)	22				
Cui et al., 2015	Healthy controls	30	T LYM	qRT-PCR	Duration of treatment, Medication,	No differences in D2R mRNA
	Psychotic not otherwise specified patients	18			Age of onset, PANSS	Significant positive correlation between D2R mRNA vs excited factor of PANSS in SCZ/schizophreniform patients
	SCZ/schizophreniform patients	14				

Abbreviations: Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Clinical Global Impression Scale (CGIS), Global Assessment of Functioning (GAF), Brief Psychiatric Rating Scale (BPRS), Abnormal Involuntary Movement Scale (AIMS). No Data (ND).

Table 3
Findings of D3R expression in LYM of patients with SCZ.

Reference	Study	n	Sample	Methodology	Clinical features	Findings
Kwak et al., 2001	Healthy controls Drug-medicated SCZ patients (»3 years) Drug-free SCZ patients (»3 months) Drug-naïve SCZ patients	31 44 28 15	PBLs	RT-PCR	Age of symptoms onset, Duration of illness, BPRS, ESRS, Dose of antipsychotic, Duration of no medication	Increased D3R mRNA (drug-free vs medicated and controls) No differences in D3R mRNA (drug-free vs drug-naïve) After taking antipsychotics, D3R peaked at 2nd week, which later at 8th decreased
van der Weide et al., 2003	Healthy controls SCZ patients	8 8	PBLs	RT-PCR	ND	No differences in D3R mRNA
Ilani et al., 2004	Healthy controls SCZ patients	11 14	PBLs	RT-PCR	ND	Increased D3R mRNA in SCZ
Vogel et al., 2004	Healthy controls Drug-naïve SCZ patients Drug-free SCZ patients (» 4 weeks) Drug-medicated SCZ patients	12 6 9 9	PBLs	RT-PCR	PANSS, BPRS, MADRS, YMRS	Reduced D3R mRNA (drug-naïve vs controls)
Rodrigues et al., 2005	Healthy controls SCZ patients	45 45	PBLs	Flow-cytometry	BPRS	No differences in D3R protein levels Significant inverse correlation (BPRS hebephrenic dimension score vs D3R)
Bonegerg et al., 2006	Healthy controls SCZ patients	10 10	Leukocyte population PBMCs	qRT-PCR	ND	Increased D3R mRNA in T cells
Kawano et al., 2011	Healthy controls SCZ patients	12 11	PBLs	qRT-PCR	PANSS, BACS-J, Treatment dose, Duration of illness	No differences in D3R mRNA D3R mRNA inversely correlated with the total PANSS score
Urhan-Kucuk et al., 2011	Healthy controls SCZ patients	51 55	PBLs	RT-PCR	ND	No differences in D3R mRNA Significant differences in D3R mRNA (controls vs disorganized SCZ, disorganized SCZ vs paranoid SCZ)
Ahmadian et al., 2014	Healthy controls Drug-naïve SCZ patients Drug-free SCZ patients (» 3 months) Drug-medicated SCZ patients (» 3 years)	20 5 15 22	PBLs	RT-PCR	ND	D3R expressed in all groups, increased mRNA in drug-free patients vs controls and significant differences between drug-naïve patients vs controls
Cui et al., 2015	Healthy controls Psychotic not otherwise specified patients SCZ/schizophreniform patients	30 18 14	T LYM	qRT-PCR	Duration of treatment, Medication, Age of onset, PANSS	Significant differences in D3R mRNA (controls vs psychotic and SCZ/schizophreniform patients)
Fernandez-Egea et al., 2016	Healthy controls Chronic SCZ patients	18 18	LYM	qRT-PCR	BMI, Smoking, BACS, CGIS	Increased D3R mRNA in clozapine-treated SCZ patients

Abbreviations: Brief Psychiatric Rating Scale (BPRS), Extrapyramidal Symptom Rating Scale (ESRS), Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Brief Assessment of Cognition in Schizophrenia (BACS), Body mass index (BMI), Clinical Global Impression Scale (CGIS). No Data (ND).

that since they are resistant to treatment, they would never reach the desired effect that reduces the symptoms of the disease.

Furthermore, negative schizophrenic or depressive symptoms and more severe psychiatric symptoms seemed to correlate with higher D3R levels (Kwak et al., 2001; Vogel et al., 2004). On the other hand, LYM D3R mRNA levels and total PANSS score showed a statistically significant inverse relationship (Kawano et al., 2011). Also there is a significant inverse correlation between BPRS hebephrenic dimension score and D3R expression in LYM of SCZ patients (Rodrigues et al., 2005).

Finally, another study revealed the presence of significantly different D3R mRNA levels in PBLs among SCZ subtypes (residual, disorganized and paranoid SCZ) per the DSM-IV criteria, leading the authors to conclude that D3R could be used as a diagnostic peripheral marker of SCZ subtypes (Urhan-Kucuk et al., 2011), although in the updated DSM-V all these different subtypes were eliminated (American Psychiatric Association, 2013).

4.2.3. D4R

In general, there are no alterations in the levels of D4R mRNA (Table 4) between SCZ patients and healthy controls in any population of leukocytes studied (Ilani et al., 2004; Rodrigues et al., 2005; Kawano et al., 2011; Ahmadian et al., 2014). However, using flow cytometry, a group of researchers observed a significant overexpression in the percentages of $CD8^+D4R^+$ and $CD4^+D4R^+$ T LYM from medicated SCZ patients institutionalized versus controls (Brito-Melo et al., 2012), and on the contrary, by RT-PCR was used to show a significant down-regulation of D4R mRNA in $CD4^+$ of SCZ patients compared to sex- and age-matched controls (Boneberg et al., 2006). The authors suggest that this difference between mRNA and protein levels might be due to post-transcriptional mechanisms or because of different populational samples. Also, since the patients in all the studies were medicated, it is unlikely that this contrast of results is caused by differences in the individual pharmacological treatment (Brito-Melo et al., 2012).

Finally, a significant inverse correlation between BPRS hebephrenic dimension score and D4R expression in LYM of SCZ patients was observed (Rodrigues et al., 2005), while D4R expression was positively correlated with the working memory subscale of the Brief Assessment of Cognition in Schizophrenia Japanese-language version (BACS-J) (Kawano et al., 2011) and the AIMS score was inversely related to $CD4^+D4R^+$ (Brito-Melo et al., 2012).

5. Conclusions

SCZ is a heterogeneous psychiatric disorder with a wide spectrum of clinical and biological manifestations. Due to the lack of objective evidence, precise diagnosis and selection of effective treatments for SCZ patients remains a challenge. Numerous technologies have been used in search of biomarkers for SCZ. However, after a century of studying SCZ their application in psychiatry remains rare and there are currently no validated biomarkers for the diagnosis and prognosis of patients with SCZ or the prediction of treatment efficacy.

Considering that in most SCZ patients suffering an acute episode, routine blood tests are usually within normal parameters, another type of analysis is necessary to detect the psychotic state. Studying DRs in the human CNS has obvious limitations. Peripheral immune cells like LYM are well-known to express all DRs on their membrane surface, and therefore, could be directly affected by DA partial agonists or antagonists, the most common antipsychotic treatment for SCZ for more than half a century. Despite the controversy, LYM are easily accessible cells from a simple blood sample, and have potential to serve as detectable peripheral molecular biomarkers to investigate neuropsychiatric diseases in living individuals. Considering the changes in DRs after taking antipsychotics, these receptors may have a physiological role, but the relationship between peripheral and central DRs is still uncertain.

This review denotes that DRs in LYM are dysregulated in certain populations of SCZ patients compared to healthy controls before taking antipsychotics and dynamically changed after taking antipsychotics, indicating that the changes in DRs expression found in SCZ patients could also result from antipsychotic medication and not from the disease itself. Further investigations into DRs in LYM are needed because they are a useful tool for evaluating the efficient properties of dopaminergic function and whether the pharmacological treatments of SCZ may be altering it. This extended analysis of the DRs status may provide the opportunity to search for factors that may account for the variance of the effect in patients, a new chance for the prediction of treatment efficiency, and detection of earlier stages of risk and prodrome of psychosis.

Table 4
Findings of D4R expression in LYM of patients with SCZ.

Reference	Study	n	Sample	Methodology	Clinical features	Findings
Ilani et al., 2004	Healthy controls SCZ patients	11 14	PBLs	RT-PCR	ND	No differences in D4R mRNA
Rodrigues et al., 2005	Healthy controls SCZ patients	45 45	PBLs	Flow-cytometry	BPRS	No differences in D4R protein levels Significant inverse correlation (BPRS hebephrenic dimension score vs D4R)
Boneberg et al., 2006	Healthy controls SCZ patients	10 10	Leukocyte population PBMCs	qRT-PCR	ND	Decreased D4R mRNA in T cells
Kawano et al., 2011	Healthy controls SCZ patients	12 11	PBLs	qRT-PCR	PANSS, BACS-J, Treatment, Dose, Duration of illness	No differences in D4R mRNA D4R mRNA positively correlated with working memory scales
Brito-Melo et al., 2012	Healthy controls SCZ patients	20 40	LYM (CD4, CD8)	Flow-cytometry	CGIS, BPRS, PANSS, AIMS, Duration of illness and hospitalization,Dose of antipsychotic	Increased percentages of $CD4^+D4R^+$ and $CD8^+D4R^+$ cells AIMS inversely related to $CD4^+D4R^+$ cells
Ahmadian et al., 2014	Healthy controls Drug-naïve SCZ patients Drug-free SCZ patients (» 3 months) Drug-medicated SCZ patients (» 3 years)	20 5 15 22	PBLs	RT-PCR	ND	D4R expressed in all groups but no differences in mRNA
Fernandez-Egea et al., 2016	Healthy controls Chronic SCZ patients	18 18	LYM	qRT-PCR	BMI, Smoking, BACS, CGIS	No differences in D4R mRNA D4R mRNA positively correlated with working memory scales

Abbreviations: Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Brief Assessment of Cognition in Schizophrenia (BACS), Clinical Global Impression Scale (CGIS), Abnormal Involuntary Movement Scale (AIMS), Body mass index (BMI). No Data (ND).

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Authors' contributions

MAP prepared the main text, tables and figure. MAP, TR-B, DP-R, JA, AB, DA-C, CF-P, MN-A, SR-G, CB-V, HJC, JMO, RCA-B contributed to specific content of the review. JA edited the article and corrected the grammar. All authors read and approved the final manuscript.

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