Dopamine Receptor

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Dopaminergic receptors (DR) including D1, D2, D3, D4 and D5, which are members of the G-protein coupled receptor family.

Parkinson's disease dopamine receptor non motor symptoms

1. Introduction

The pathological hallmark of Parkinson's disease (PD) is represented by the degeneration of the dopaminergic neurons in the pars compacta of the midbrain substantia nigra. Cell loss is accompanied by the accumulation of alpha-synuclein (α-syn) and it is currently believed that α-syn accumulation is correlated with PD progression [1]. Currently, the gold standard treatment for PD consists of dopamine (DA) replacement therapy (DRT) aiming at counterbalancing DA loss caused by nigrostriatal degeneration. Accordingly, the most used drugs for PD treatment are the DA precursor Levodopa, alone or together with MAO-B and COMT inhibitors, and DA-agonists. Unfortunately, as disease progresses, the benefits of symptomatic therapies tend to wear off [2] and to be counterbalanced by the onset of side effects and complications [3]

There are five types of DR, D1, D2, D3, D4 and D5, which are members of the G-protein coupled receptor family [4]. The dopaminergic receptor (DR) subtypes are divided into two families according to their pharmacological profile and second messenger coupling: the "D1-like", including D1 and D5 which activate adenylate cyclase, and "D2-like" including types D2, D3 and D4 which inhibit adenylate cyclase [5]. The final effect of D1-like activation (D1 and D5) can be both excitation (via opening of sodium channels) and inhibition (via opening of potassium channels), while the ultimate effect of D2-like activation (D2, D3 and D4) is inhibition of target neuron [6].

D1 receptors are the most abundant DR in the human nervous system followed by D2 and other DR (D3, D4 and D5) whose levels are significantly lower [6].

Despite the key role of dopaminergic pathways in the pathogenesis as well as in the pharmacotherapy of PD, evidence on the role of genetic polymorphisms in DR and related pathways is still fragmentary. In this regard, several functional single nucleotide polymorphisms (SNPs, i.e., DNA sequence variations occurring when a single nucleotide in the genome differs between paired chromosomes), the most common type of polymorphisms in the human genome, have been identified in dopamine receptor genes (DR) [7][8]. Among these SNPs, some have been related with other neuropsychiatric conditions such as schizophrenia [9][10], attention deficit hyperactivity disorder [11][12], addictions [13] and even to clinical aspects of PD [14][15].

Furthermore, DR play a key role in the regulation of peripheral immunity [16][17][18] and recent findings suggest a role for the peripheral immune response in PD. For example, it has been shown that α-syn is recognized by T cells, thus suggesting a relationship between protein deposition, neuronal loss and immune response [1][19]. Since immune cells express DR, it is reasonable to suppose that SNPs in genes coding for these receptors could modulate functions of these cells. In this regard, it has been recently suggested that SNPs in DRs could influence immune cell functions in different ways [20][21]. Nonetheless, the relevance of such effects on PD development and progression, including response to therapy, has never been examined so far.

2. Role of Dr Genetic Polymorphisms in Peripheral Immunity: Possible Relevance for Pd

Besides a more “direct” action in determining clinical progression of PD and drugs response, DR SNPs may also play an indirect role by modulating the peripheral immune response, which is involved in the pathophysiology of PD [16][17][18], therefore representing a potential therapeutic target for disease modification [22].

DA is a crucial transmitter in the neuro-immune network, and dopaminergic pathways have received increasing interest in the study of adaptive immunity. DA is able to modulate activity of several immune cell subpopulations such as: T and B cells, dendritic cells, macrophages, microglia, neutrophils as well as NK cells (reviewed in [17][23]). Moreover, immune cells express all DRs, with a higher expression of D1-like receptors. Particularly, different cell sub-populations may express different receptors patterns: D1-like receptors are more represented in naïve T cells, while D2-like receptors are more expressed in memory cells [20]. Among immune cells, CD4+ T cells are specifically affected by DA, which subserve an inhibitory loop in human CD4+ CD25 high regulatory T lymphocytes. This specialized T cell subset plays a key role in the control of immune homeostasis [24] and mediates the influence exerted by dendritic cells on the differentiation of naive CD4+ T cells. In PD animal models, these regulatory cells (Treg) are able to modulate microglia differentiation and therefore influence the neurodegenerative process. Particularly, they can modulate microglia proteomics, reducing the expression of protein involved, among others, in cell metabolism and migration and protein degradation [25], and attenuate the Th17-mediated dopaminergic neuronal loss [26]. Furthermore, Treg are reduced in 6-OHDA mice model of PD and this reduction correlates with the central change in microglia profile toward a pro-inflammatory one [27].

PD patients present changes in peripheral cells expression: different studies reported a lower lymphocyte count related to a reduced number of helper CD4+ T cells and B cells [28][29]. Recently, it has been demonstrated that in a large cohort of UK subjects, a lower lymphocyte number represents an important risk factor for a subsequent diagnosis of PD [30]. Additionally, it has recently been suggested that *DR* SNPs could influence immune cell functions in different ways. rs4532 and rs686 in *DRD1* and rs6283 in *DRD5*, alone and in combination, were associated with total count of lymphocytes, as well as CD3+ and CD4+ T lymphocytes, thus indicating a prevalent functional activity of D1-like receptors on these cells [20]. Moreover, SNPs in *DR* including rs4523 affect Treg-induced decrease of Teff cell proliferation in healthy controls [21].

PD patients display a pro-inflammatory peripheral immune phenotype, with a production of cytokines leading to Th1 differentiation [19]. Moreover, presence of circulating auto-antibodies and T cell infiltration in CNS were found in PD subjects [31]. It was suggested that infiltration and reactivation of T cells can prime microglia into a pro-inflammatory phenotype, which can in turn trigger a further detrimental response in the CNS, thus perpetuating the ongoing neurodegenerative process of PD [16]. More recently, experimental work provided evidence on the involvement of immune dysfunction in the development of both motor and non-motor symptoms of PD, including dyskinesia [32], RBD [33] and cognitive decline [34].

Altogether, these findings underline that polymorphisms in *DR* would likely play a role in the immune crosstalk of PD.

Although preliminary in the field of neuro-immunomodulation in PD, the above reported examples stress the importance of the possible role of genetic differences in dopaminergic modulation of immune systems in PD. In our opinion, future investigations in this field may provide a better understanding of PD pathophysiology, and eventually help the identification of new therapeutic targets for this disease [35]

3. Conclusions

All these data highlight the importance of personal genetic predisposition in the pathophysiology of PD.

Particularly, *DR* SNPs may be involved not only in disease development, but also in motor and non-motor complications (dyskinesia, visual hallucinations, ICD and cognitive decline), as well as in pharmacological response and side effects induced by dopaminergic agents. Furthermore, they may modulate peripheral cells expression contributing to the creation of an impaired peripheral immunity system, which is known to play a crucial role in the pathophysiology of PD [36].

DRD2 and DRD3 SNPs represent the most promising DR genetic variations in terms of biomarkers identification. Among them, DRD2 rs1800497 and DRD3 rs6280 should be tested in large cohorts of PD patients in order to better clarify their contribution in disease progression.

The evaluation of the relationship between PD progression, response to antiparkinsonian drugs and patients' genetic profile could be useful in clinical practice since it can help in determining biomarkers for disease evolution at the time of diagnosis and personal response to pharmacological treatment. This approach will be determinant in the creation of a causative and tailored pharmacological approach which, in addition to providing benefits for patients, would reduce the management costs of therapy.

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