The Cross-Talk Between the Dopaminergic and the Immune System Involved in Schizophrenia

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Dopamine is one of the neurotransmitters whose transmission is altered in a number of neural pathways in the brain of schizophrenic patients. Current evidence indicates that these alterations involve hyperactive dopaminergic transmission in mesolimbic areas, striatum, and hippocampus, whereas hypoactive dopaminergic transmission has been reported in the prefrontal cortex of schizophrenic patients. Consequently, schizophrenia is associated with several cognitive and behavioral alterations. Of note, the immune system has been found to collaborate with the central nervous system in a number of cognitive and behavioral functions, which are dysregulated in schizophrenia. Moreover, emerging evidence has associated schizophrenia and inflammation. Importantly, different lines of evidence have shown dopamine as a major regulator of inflammation. In this regard, dopamine might exert strong regulation in the activity, migration, differentiation, and proliferation of immune cells that have been shown to contribute to cognitive functions, including T-cells, microglial cells, and peripheral monocytes. Thereby, alterations in dopamine levels associated to schizophrenia might affect inflammatory response of immune cells and consequently some behavioral functions, including reference memory, learning, social behavior, and stress resilience. Altogether these findings support the involvement of an active cross-talk between the dopaminergic and immune systems in the physiopathology of schizophrenia. In this review we summarize, integrate, and discuss the current evidence indicating the involvement of an altered dopaminergic regulation of immunity in schizophrenia.

Keywords: schizophrenia, dopamine receptors, T cells, microglia, peripheral monocytes, neuroimmunology, behavior

DYSREGULATION OF THE DOPAMINERGIC NEURAL PATHWAYS IN THE SCHIZOPHRENIA

Schizophrenia is a mental illness that often appears during late adolescence or early adulthood. It is characterized by thought disorders, perception, cognition and volition. The prevalence of this disorder reaches almost 1% of the world population, with an annual incidence ranging between 3.89 and 4.03 per 1,000 subjects (Moreno-Kustner et al., 2018). Its etiology is still unclear, and includes genetic and environmental components promoting alterations of dopaminergic signaling. The initial dopamine
hypothesis stated that hyperactive dopaminergic transmission leads to development of schizophrenia symptoms (hallucinations, delusions, thought disorder, among others). However, several lines of evidence have shown that hypoactivity of frontal dopaminergic neurons in rodents (Pycock et al., 1980), non-human primates (Roberts et al., 1994), and humans (Ragland et al., 2007; Simpson et al., 2010) are also associated with schizophrenia. For instance, a pharmacological lesion of subcortical dopaminergic pathways in rats suggested a correlation between hyperactivation of subcortical dopaminergic neurons with hypoactivity of frontal dopaminergic neurons (Pycock et al., 1980). In addition, evidence obtained from humans has suggested that the polymorphism in the gene encoding catechol-O-methyltransferase, an enzyme involved in the degradation of dopamine, is associated with hypoactivity of prefrontal dopaminergic neurons in schizophrenia (Slifstein et al., 2008). Moreover, patients with frontal lobe damage as well as schizophrenia patients display similar alterations in the executive function (Ragland et al., 2007). Therefore, the current dopaminergic hypothesis involves hyperactive dopaminergic transmission in mesolimbic areas, striatum and hippocampus (Lodge and Grace, 2007; Patel et al., 2010; Weinstein et al., 2017), as well as hypoactive dopaminergic transmission in the prefrontal cortex of schizophrenic patients (Da Silva Alves et al., 2008). In addition, glutamatergic hypofunction has been suggested as one of the mechanisms involved in this dopaminergic dysfunction in schizophrenia (Swedlow et al., 2009). In this regard, it has been hypothesized that DRD2-antagonism might prevent DRD1-mediated potentiation of N-Methyl-d-aspartate (NMDA) responses in the prefrontal cortex (Paz et al., 2008). Another line of evidence points to the changes in subcortical dopaminergic activity as one of the responsible circuits promoting alterations in glutamatergic neurotransmission in the substantia nigra (Mueller et al., 2004).

This, imbalance in the dopaminergic signaling has been differentially associated with the development of positive (presence of undesired cognitive/emotional functions, such as hallucinations, delusions, thought disorders, trouble concentrating, movement disorders) and negative (deficiency of desired cognitive/emotional effects, such as flattened affect, lack of pleasure, trouble with speech, apathy, concentration problems, and lack of motivation) symptoms. Positive symptoms have been related with stimulation of D2-like receptors, including DRD2, DRD3, and DRD4 (Li et al., 2016). Both primate and rodent brains express a higher density of D1-like (including DRD1 and DRD5) than D2-like receptors in healthy conditions (Weinstein et al., 2017). Meta-analysis of studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown that presynaptic dopamine release is decreased in most brain regions of schizophrenic patients (Slifstein et al., 2015), except in the striatum, where the synthesis and the levels of dopamine released are increased (McCutcheon et al., 2018; Avram et al., 2019). Furthermore, PET studies have demonstrated that prefrontal DRD1 expression is decreased in patients with schizophrenia (Kosaka et al., 2010), which has been associated with working memory deficits in the prefrontal cortex (Takahashi et al., 2008). In contrast, DRD1 expression is increased in the temporal and parietal cortex of schizophrenic patients, which might be associated with auditory halluciinations (Domyo et al., 2001). It has been described a moderate increase (10–20%) in the expression of DRD2 and DRD3 in the striatum of a subgroup of schizophrenic patients (Kestler et al., 2001). Moreover, DRD3 expression has been found to be enhanced in the basal ganglia, ventral forebrain (Gurevich et al., 1997), and blood lymphocytes of schizophrenic patients (Ilani et al., 2001). On the other hand, it has been shown that in comparison to healthy subjects, dopamine occupies a higher proportion of striatal D2-like receptors (Kegeles et al., 2010), and a bigger fraction of the dopamine transporters (DAT) in sensorimotor striatum (Weinstein et al., 2017) in schizophrenia.

Interestingly, it has been described a sub-regional heterogeneity in the dopaminergic dysregulation within the striatum. The greatest alterations in dopaminergic transmission have been observed in the associative striatum region. These alterations have been negatively correlated with verbal fluency performance in schizophrenic patients (Howes et al., 2009b). Since this brain region regulates information flow to and from the prefrontal cortex, the authors have suggested a potential link between striatal dopaminergic dysfunction and prefrontal alterations in schizophrenic patients (Howes et al., 2009b). A recent study showed that impaired connectivity between the cortico-striato-thalamo-cortical circuits is associated with cognitive difficulties in schizophrenic patients, including deficits in attention, memory, and executive function (Avram et al., 2018). Moreover, reduced striatal dopamine synthesis correlates with cognitive difficulties in patients during remission of positive symptoms, without an association with negative symptoms (Avram et al., 2019). Of note, the cohort of patients was taking antipsychotic drugs that did not seem to have a short-term clear effect on the results of the study (Avram et al., 2019). In addition, studies performed in schizophrenic patients have analyzed the expression levels of tyrosine hydroxylase (TH), the enzyme that catalyzes the first (and limiting) step in the biosynthesis of dopamine, and have found heterogeneous results, supporting either dopaminergic hyperactivity or hypoactivity (Akil et al., 2000; Mueller et al., 2004). One study has reported regional and laminar specific decrease of TH-immunoreactive axons in the entorhinal cortex of schizophrenic patients (Akil et al., 2000), whereas another study has shown increased TH mRNA levels in the dopaminergic neurons of the substantia nigra pars compacta of schizophrenic patients (Mueller et al., 2004).

Thus, current evidence indicates the involvement of complex alterations in the activity of neural dopaminergic pathways in the brain of schizophrenic patients, which are not completely consolidated. Therefore, further research is still needed to better understand the alterations of dopaminergic circuitry associated to the pathophysiological scenario of schizophrenia.

TARGETING THE DOPAMINERGIC SYSTEM IN SCHIZOPHRENIA

The World Health Organization estimates that costs of schizophrenia in Western countries represent 1.6–2.6% of total health care budget, whereas in the US more than $60 billion USD per year are spent in this disorder (Howes et al., 2009a; Chong et al.,