PERSPECTIVE

Atypical antipsychotics, more than just an antipsychotic

Antipsychotics are the prescribed drugs for schizophrenia. The first substance used for antipsychotic purposes appeared in 1952 and it was a general anesthetic: chlorpromazine. The use of this drug was mainly because of its effects on violent behavior instead of sedation in patients, which "controls" the psychotic episodes and prevents psychosis relapse. Since then, pharmaceutical antipsychotics have been developed, producing second-generation or atypical drugs. These drugs arose with the synthesis of clozapine in the late '50s, which represented (and still represent) the "guide molecule" for the development of these substances, because of its effectiveness on the symptomatology of the disease. Atypical antipsychotics have a high affinity for serotonergic 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptors and a moderate affinity for dopaminergic D_2 receptors (**Figure 1**). Thus, these drugs effectively attenuate psychotic episodes, hallucinations, and delusions (positive symptomatology of the disease) with a low probability of generating movement disorders (extrapyramidal symptoms), which differentiate them from the typical antipsychotics. However, atypical antipsychotics have modest effects on negative symptomatology (anhedonia, apathy, social withdrawal) and fail to counteract cognitive deficits. Also, many atypical antipsychotics trigger alterations in carbohydrate and lipid metabolism and cause side effects. This is because of its non-specific pharmacodynamics since atypical antipsychotics have an affinity for histaminergic, muscarinic, and adrenergic receptors, as well as other isoforms of serotonergic and dopaminergic receptors rather than the 5-HT_{2A} and D_2 receptors. Thus, this "promiscuous" pharmacology of atypical antipsychotics has led to the discovery of other mechanisms that represent potential therapeutic targets in schizophrenia (Aringhieri et al., 2018).

Schizophrenia is considered as a neurodevelopmental disorder involving excessive synapses elimination during adolescence, presumably because of microglia hyperactivity and aversive micro-environmental conditions. Pathophysiological mechanisms, such as oxidative/nitrosative stress, can cause this to happen, therefore neurotrophic and antioxidant substances are potential therapeutic drugs for schizophrenia.

Reproducing some behavioral, neuroanatomical or neurochemical schizophrenia-related characteristics in mice or rats help us to analyze some mechanisms of antipsychotics to clarify how they are working in the brain and understand some mechanisms of the neurobiology of the disease, and consequently develop more efficient drugs. It is a fact that animal models represent a very useful but also a limited tool to understand the pathophysiology of schizophrenia. Not only because these models reproduce few characteristics of the disease, but also because the created phenotype can be associated with other neurodevelopmental disorders, such as autism.

In 1993, Lipska and Weinberger described a developmental schizophrenia-related model with some features of the disease: the neonatal ventral hippocampus lesion (NVHL) in the rat. The early life ventral hippocampus disconnection triggers abnormal connectivity with other cortical structures, such as the basolateral amygdala and the prefrontal cortex (PFC). These structures are part of the corticolimbic system that associates with internal and external stimuli to evoke a behavioral response. Thus, PFC function is not only compromised by disrupted connectivity to the hippocampus, but also by the aberrant limbic-motor integration which is modulated by the ventral striatum. It receives glutamatergic axons from cortical structures and also has large dopaminergic innervation from the ventral tegmental area, constituting the mesolimbic pathway. Thus, increased mesolimbic activity generates excessive stimulation of the projection spiny neurons in this area, which used γ-aminobutyric acid as the main neurotransmitter. In such a manner, ventral striatum inhibits the ventral pallidum, which in turn inhibits the dorsomedial thalamus so that activity closes the loop innervating the PFC. These neuroanatomical and neurochemical disruptions of the corticolimbic system in rats with NVHL trigger diverse post-pubertal behavioral abnormalities associated with positive symptomatology like the onset of psychosis in schizophrenia, which is corrected after atypical antipsychotic administration (**Figure 1**) (Tseng, 2009). Also, the rats with NVHL have several structural plasticity disturbances in the PFC, such as the retraction of the basilar dendritic arbor in the pyramidal cells of this region. Pyramidal neurons have fewer dendritic spines, specifically mushroom-shaped spines, due to a pathology in the dendritic spines, which is one of the few prevalent pathophysiological data in schizophrenia (Tendilla-Beltrán et al., 2019a). It is known that the neural morphology alterations disrupt functions in the PFC in animals with NVHL. Our group has reported the capability of atypical antipsychotics (clozapine, risperidone, and unpublished data of olanzapine) and a neurotrophic-like substance called "cerebrolysin" to ameliorate the neural atrophy of PFC neurons, and these cellular improvements promote some behavioral corrections in NHVL animals (Bringas et al., 2012; Vázquez-Roque et al., 2012; Tendilla-Beltrán et al., 2019b). Also, we demonstrated that dendritic arbor atrophy, deficient spinogenesis, and impairment in the maturation of dendritic spines are a consequence of the brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) pathway disruption, and risperidone treatment reverses it (**Figure 1**) (Tendilla-Beltrán et al., 2019b). Moreover, there is oxidative/nitrosative stress in the PFC of rats with NVHL, another relevant pathophysiological cue in schizophrenia (Cabungcal et al., 2014). Oxidative/nitrosative stress is the imbalance of antioxidant molecules (reduced) and free radicals (increased) that ultimately lead to cell damage (Leza et al., 2015). In the PFC in NVHL rats, there are elevated nitric oxide and cyclooxygenase-2 (COX-2) protein levels, both pro-oxidant mediators; and the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant pathway is altered (**Figure 1**) (Tendilla-Beltrán et al., 2019b). Nrf2 is a nuclear factor that when translocated to the nucleus acts on the antioxidant response elements in the DNA to promote the synthesis of antioxidant enzymes, such as glutathione peroxidase and catalase, whose expression is reduced in the PFC of adult NVHL animals (**Figure 1**) (Hui et al., 2019). Interestingly, O'Donnell's group and ours have reported that both risperidone and antioxidant treatments suppress oxidative/nitrosative stress in the PFC of rats with NVHL (Cabungcal et al., 2014; Tendilla-Beltrán et al., 2019b). The mechanisms of oxidative/nitrosative stress in the model are still unclear, but COX-2 and nitric oxide-related pathways could cause this type of stress. Recently, we reported that COX-2 levels increase in the PFC of NVHL animals. COX-2 has a dual effect; it can produce free radicals and consequently oxidative/nitrosative stress,

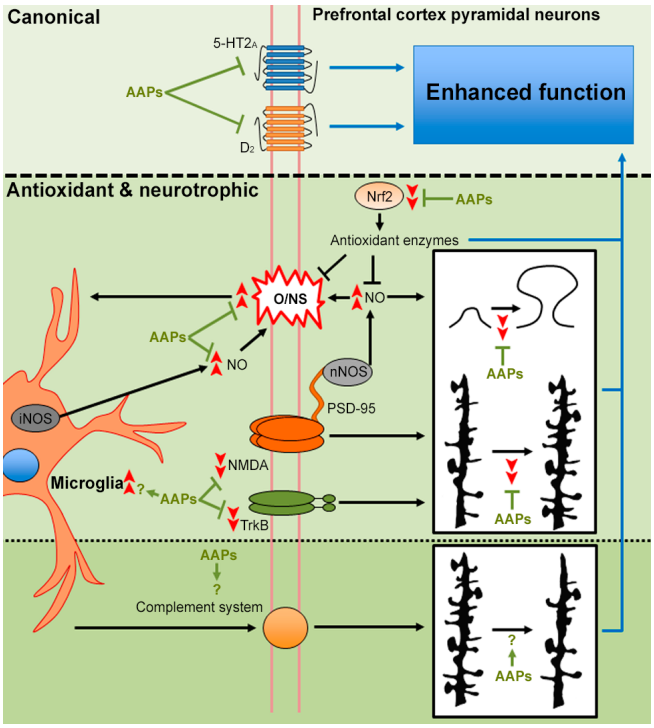

Figure 1 Atypical antipsychotic (AAP) mechanisms (shown in green) on the prefrontal cortex alterations of neonatal ventral hippocampus lesioned animals (red arrowheads).
The canonical mechanisms of atypical antipsychotics include the antagonism of D_2 and 5-HT_{2A} receptors. Moreover, other mechanisms are implied in the effectiveness of these substances, such as antioxidant and neurotrophic effects, including the restoration of the Nrf2 pathway that promotes the synthesis of antioxidant enzymes, which attenuates oxidative/nitrosative stress (O/NS). Nitric oxide (NO) is necessary for dendritic spine maturation, but leads to O/NS at excessive levels. Microglia is the main NO source in the inflammatory response and also eliminates synapses via the complement system, the effect of APPs on this system is still unknown. There are neurotrophic effects of AAPs throughout the BDNF/TrkB pathway which improve NMDA function. Altogether, these mechanisms improve the prefrontal cortex function in rats with NHVL. 5-HT_{2A}: 5-Hydroxytryptamine receptor 2A; BDNF/TrkB: brain-derived neurotrophic factor/tropomyosin receptor kinase B; iNOS: inducible nitric oxide synthase; NMDA: N-methyl D-aspartate glutamate receptor; nNOS: neural nitric oxide synthase; Nrf2: nuclear factor (erythroid-derived 2)-like 2; PSD-95: postsynaptic density protein 95.

and also induce glutamate neurotoxicity via astrocytes. It can also have antioxidant effects specifically inducing the synthesis stimulation of the prostaglandin 15-deoxy-PGJ2, which is a potent anti-inflammatory mediator in the brain (Leza et al., 2015). However, further studies must explore the mechanisms of COX-2 mediated pathways. Regarding the nitric oxide, we have demonstrated an increased nitrite (the stable metabolite of nitric oxide) concentration in the PFC, which is interestingly reduced by typical and atypical antipsychotics (**Figure 1**) (Negrete-Díaz et al., 2010; Bringas et al., 2012; Tendilla-Beltrán et al., 2019b). Risperidone treatment reduces COX-2 protein levels and lipid peroxidation, which represents a physiological effect of oxidative/nitrosative stress, and restores the Nrf2 pathway, associated with the enhancement of structural plasticity of PFC pyramidal cells in this rodent model (**Figure 1**) (Tendilla-Beltrán et al., 2019b).

Oxidative/nitrosative stress can not only be associated with direct neural rearrangement but can also promote the activation of microglia, which are the main cells involved in synapse elimination. The Srivastava group reported an excessive microglia population and phagocytic activity in the PFC of NVHL animals. Interestingly the administration of minocycline, an inhibitor of microglial activation, improves the sensory gating performance of NVHL rats (Hui et al., 2019). This represents a new scope for the model since recent reports maintain that excessive synaptic pruning via microglia-elimination mechanisms underlies the pathophysiology of schizophrenia (Sellgren et al., 2019). Nevertheless, there is no information about the effects of the atypical antipsychotics in microglia synapse-pruning mechanisms (**Figure 1**).

Interestingly, since the start of clozapine clinical use (in the '70s), the mechanism of the atypical antipsychotics is still the same and also, still produces side effects. Several efforts have been made to design novel drugs with new pharmacological targets. One example is the agonists for glutamatergic transmission (for N-methyl D-aspartate glutamate receptor and some group II metabotropic receptors) to ameliorate schizophrenia symptomatology, but the development of these drugs still has a long way to go because of the clinical-trial failure (Aringhieri et al., 2018). Knowing that glutamate activity is also involved in neuroplasticity, it seems that substances with antipsychotic effects have some neural plasticity-related effects in common.

The aforementioned atypical antipsychotic mechanisms make us question whether neuroplasticity and oxidative/nitrosative stress pathways converge at some point in schizophrenia. We think they do, and the nitric oxide system could be a possible link, since the inducible isoform of the nitric oxide synthase is overexpressed by microglia in the inflammatory response [for review see Leza et al. (2015)]. Neural isoform activity is also necessary for the maturation of dendritic spines in the neocortex; and antipsychotics modulate this system, as previously mentioned. Thus, the molecules and cells involved in the process in which the nitric oxide system goes from having a synaptic plasticity effect to causing oxidative/nitrosative stress need to be studied (**Figure 1**). Another doubt is whether it is possible to develop more specific antipsychotic drugs. Until the mechanisms of the schizophrenia pathophysiology are clear, this is not going to happen. But nowadays neural plasticity or antioxidant-related pathways represent promising pharmacological targets. However, it is not an easy task, as the description of the mechanisms associated with these signaling pathways must be detailed. For example, regarding the BDNF/TrkB pathway, we need to know whether atypical antipsychotics stimulate the synthesis or liberation of BNDF. Moreover, we reported that risperidone increased the protein levels of the TrkB full-length isoform, which is the functional one, in the PFC of NVHL rats. We are still unsure whether the aforementioned are common mechanisms of atypical antipsychotics or if they have synergic effects, but it seems that canonical, antioxidant and neurotrophic effects altogether improve PFC function in the NVHL model (**Figure 1**). However, there are still some challenges. One of them is that most of these effects must be localized to specific brain areas such as the PFC, the ventral striatum or the basolateral amygdala. Another one is the development of drugs that generate fewer side effects, which represent one of the main problems for patients. Thus, antipsychotic development also needs to focus on this issue, and looking for other targets apart from dopaminergic and serotonergic ones could be helpful in resolving this.

It is important to note that neural plasticity underlies the neurobiology of other mental diseases, such as major depressive disorder, and interestingly various antidepressive drugs have an effect on synaptic plasticity with several action mechanisms, including BDNF and N-methyl D-aspartate glutamate receptor-related signaling pathways (Duman et al., 2016).

In summary, PFC neuroplasticity disruption is involved in schizophrenia pathophysiology and is reproduced in rats with NVHL, a developmental schizophrenia-related model. Atypical antipsychotics correct behavioral alterations and restore neural atrophy in the PFC of NVHL animals with neurotrophic and antioxidant effects. Therefore, there is enough evidence to consider neuroplasticity, as well as oxidative/nitrosative pathways, common mechanisms of atypical antipsychotics. This could open new perspectives for the development of more effective and specific drugs for schizophrenia treatment.

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