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Abdelaziz Ghanemi

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REVIEW ARTICLE

Schizophrenia and Parkinson's disease: Selected therapeutic advances beyond the dopaminergic etiologies

Abdelaziz Ghanemi *

Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China
Department of Pharmacy, Faculty of medicine, Mentouri University of Constantine, Constantine 25000, Algeria

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Abstract Both Schizophrenia and Parkinson's disease are very much linked to the dopaminergic system, yet a larger understanding that goes behind this "simplified explanation" of the linked phenomena remains important to further novel advances. The description of factors related to both disorders including implicated receptors, the involved neurotransmitters and enzymes, pharmakons' properties and the related symptoms and dysfunctions might have diverse consequences, mainly, the new therapeutic implications which lie on the pharmacological applications via the pathogenesis explanations and the identification of new possible targets, in addition to the potential development of new researches' methods.

1. Introduction

Considering each of Schizophrenia and Parkinson's disease as a simple dopaminergic system imbalance or dysfunction is far from being a complete understanding of the two neural diseases. Within the coming paragraphs we intend to explain via illustrative selected examples how the *in vivo* interactions between neuronal and chemical networks (including enzymes and non-enzymatic molecules) contribute in generating some of the pathogenesis and explain a part of the related processes observed in both schizophrenia and Parkinson's disease. Through the bibliographic research we felt a need for descriptions with a non-dopaminergic approach to further identify new targets to control the two diseases and this is the purpose of the commentaries we have summarized herein.

2. Schizophrenia: network dysfunctions and new properties of the antipsychotic agents

Schizophrenia (SZ) may be considered as progressive and neurodegenerative.[1] SZ has been linked to dopaminergic function, in fact in addition to a reduced dopamine reuptake transporter (DAT) expression in SZ brains.[2] Hyperdopaminergic function is also reported in SZ[3] thus, drugs effective in treating SZ have anti-dopaminergic properties.[4–6] The antipsychotics (APs) (used for the treatment of Schizophrenia) block dopamine D2 receptor (DRD2) and thus produce AP-related neurotoxic effects[7,8] that are mainly resulting from extrapyramidal

* Present address: Department of Pharmacology, China Pharmaceutical University, No. 24 Tong Jia Xiang, Nanjing 210009, Jiangsu Province, The People's Republic of China. Mobile: +86 13776688144.
E-mail address: ghanemiabdelaziz@hotmail.com
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symptoms (EPS) and tardive dyskinesia (TD),[1] moreover haloperidol, a reference first-generation antipsychotic (FGA), has been shown to enhance caspase-3 activity in cortical neurons[9] and this in addition to EPS risk contribution results from the action of antipsychotics on 5-hydroxytryptamine (5-HT) receptors, thus the use of ketanserin, a 5-HT2A antagonist suppresses the neuronal apoptosis induced by haloperidol.[9] In contrast, a paper published in 2008 pointed out the neuroprotective effect that some second generation antipsychotics (SGA) can potentially have.[10] Furthermore, SGAs protect SHSY5Y cells against serum withdrawal-induced apoptosis,[11] indeed, haloperidol and the other first-generation antipsychotics (FGA), produce more EPS than SGAs and the affinity of FGA for DRD2 is higher than SGAs,[12,13] furthermore FGA affect neuronal cells by causing apoptosis, necrosis and oxidative stress[14,15] and therefore modify the bioavailability of the neurons.[16]

To find out more lines of evidence for the neuroprotective effects of SGAs a recent comparative study[1] has shown differences between three APs: haloperidol, and two second generation antipsychotics, risperidone and paliperidone (9 hydroxyrisperidone). The study used the dopaminergic cell model (neuroblastoma cells SK-N-SH), and did a neurotoxic/neuroprotective activity analysis. The results pointed out that haloperidol is likely to produce apoptosis whereas risperidone and paliperidone may have neuroprotective effects,[1] furthermore, with risperidone we have less EPS than those observed with haloperidol thus, at high doses risperidone can be a conventional antipsychotic.[17] To complete our data we need to further carry out new researches to compare both neurotoxic and eventually neuroprotective effects with other SGAs (clozapine or olanzapine) that have less potential to produce EPS.[1] On the other hand, in addition to altered glutamate, serotonin and dopamine, glutamate functions, have been linked with SZ pathophysiology.[3,18–20] Moreover, for excitatory amino acid transporters (EAATs), a family of five subtypes in humans termed EAAT1–EAAT5[21] are involved in both the clearance of glutamate and reducing N-methyl D-aspartate (NMDA) function,[22–25] it has been shown that suppressing the transcription of brain EAAT1–EAAT3[26,27] enhances glutamate contents and reduces hypoglutamatergic symptoms that exist in SZ. Thus it has been pointed out that details about EAATs that are involved in glutamatergic transmission can make EAATs a potential therapeutic targets for treating SZ.[28] We mention also that toxicological aspects have to be taken into account, in fact antipsychotic treatment has been linked with increased superoxide dismutase (SOD)[29,30] and enhancement of free radical synthesis.[31] Furthermore olanzapine, clozapine, quetiapine and risperidone have been shown to modulate the expression of the potent antioxidant SOD1.[32] Therefore further data about the influence of antipsychotic drugs on SOD and the resulting oxidative stress are needed.[30] The previous elements show a new viewpoint about schizophrenia, we can consider it as a psychosis or as neurodegenerative, as we treat it by antipsychotics and some of them show neuroprotective properties (risperidone and paliperidone), such discoveries in addition to the properties of suppressing EAAT transcription and modulating SOD expression may be considered either as inclusion or exclusion factors to choose the most appropriate antipsychotic agent that will treat SZ with less side effects and neurotoxic consequences. Importantly the pathological profile, which is mainly the existence or the non existence of other neurological disorders for the SZ patients, must also be taken into account while selecting the most appropriate antipsychotic for SZ treatment.

3. Parkinson's disease: neuro-viability-related drugs' properties

Parkinson's disease (PD), with a prevalence of 0.3% of the entire population,[33] is characterized by movement disorder resulting essentially from neurolysis affecting dopaminergic neurons in the substantia nigra pars compacta (SNpc).[34] Furthermore several neuro-structures, such as anterior olfactory structures, amygdala, dorsal motor nucleus of vagus, caudal raphe nuclei, locus coeruleus, autonomic nervous system, hippocampus, and cerebral cortex have been linked to PD[35] and thus, supposing the role of several neurotransmitters in PD. PD has, in addition to motor symptoms, non-motor symptoms including olfactory and memory impairments, sleep abnormalities, anxiety and depression, as well as gastrointestinal disturbance, likely because cholinergic, adrenergic and serotonergic neurons are lost.[36] Other papers emphasized more precisely depression and anxiety as symptoms,[37,38] on the other hand, dopaminergic therapy (mainly used in PD) does not treat non-motor symptoms.[36] Moreover numerous publications specified the existent links between PD and anxiety.[39–46] Supposing that anxiety and PD have common mechanisms, in many cases anxiety is neglected when treating PD patients.[42]

To further illustrate the neuronal network involved in PD we describe other neurotransmitters' involvement in anxiety in PD patients, in fact we have the suppression of both dopaminergic transmission and the activity at DA receptors that were linked to social phobia,[47–50] perturbation of dopaminergic input to the amygdala[51,52] and it has been shown that noradrenergic and serotonergic systems are also implicated.[53]

In addition, serotonergic cell loss in the raphe nuclei was also reported[35,54] and dysfunctions in serotonin (5-HT) may result in anxiety disorders.[55] Furthermore noradrenaline (NA) dysfunction was also shown in PD patients.[35,56] Anxiety disorder-related transmitters include gamma aminobutyric acid (GABA) and glutamate[55] while PD patients have shown abnormalities of these two neurotransmitters[57–59] showing the importance of anxiety disorder in PD. In fact the severity of anxiety lies in the fact that it deteriorates parkinsonian symptoms,[60] thus showing the importance of its treatment. Many therapeutical tools are currently in use to deal with anxiety disorders in PD,[61] thus, from a pharmacological viewpoint several remarks must be considered, for example the anxiety may be the result of antiparkinsonian medication, thus we need to change the therapy or even to reduce the dose[62] before anxiolytic use, to adjust the anti-parkinsonian therapy.[63] Furthermore, recent studies pointed out the potential of the drugs that modulate the activity of GABA and glutamate neurotransmitter systems to treat anxiety disorders in PD[64–68] but further data are still required to find out the best therapeutical approach for anxiety in PD.[69]

PD researches focused mainly on neuroprotective agents and, somehow, neglected non-motor symptoms. Some symptoms like anxiety are not, as it might be believed, necessarily secondary to the psychosocial stress related to the disease[61] but an independent pathology. PD's both motor and

non-motor symptoms have been linked to several neurotransmitter systems (dopamine, noradrenalin, GABA, serotonin and acetylcholine) thus we may think about the use of agonists or antagonist of those neurotransmitters to develop a new treatment via new targets by reconsidering the neuronal network dysfunctions during PD which is far from being limited to the dopaminergic systems.

On the other hand adenosine receptor with its four subtypes – adenosine A1, A2A, A2B and A3 – that belongs to the G protein coupled receptors (GPCRs)[70] has been shown to play a role in numerous neurological diseases including Parkinson's disease thus, has been considered as possible targets to treat those diseases and also to treat pain, insomnia and drug addiction.[71]

Moreover, it has been suggested that there is a lower risk of Parkinson's disease for coffee and tea consumers[72] and naturally occurring methylxanthines, including caffeine and theophylline, inhibit the activity of the adenosine A1, A2A, and A2B receptor subtypes[73] and thus influence locomotor behavior and neurotransmitter release in the basal ganglia[74,75] showing the existent link between Parkinson's disease and adenosine receptor. In addition, it reflects also the importance of the adenosine system in the basal ganglia. Importantly, it has been reported that ZM241385, a nonxanthine triazolotriazine synthetic adenosine A2A receptor antagonist, increases L-DOPA derived dopamine release.[76,77] Thus, many adenosine A2A receptor antagonists have been developed, they may probably constitute pharmacological arsenal for the control of impairment of motor skills observed in patients suffering from Parkinson's disease.[70]

4. Perspectives

Getting new data from a different field has allowed us to have a larger understanding of both Schizophrenia and Parkinson's disease and to realize the complex network dysfunctions they implicate rather than the limited description of simple imbalances between limited neurotransmitters. Thus, the given new aspects and concepts, if well investigated and completed with new properties that can influence the systems' functions such as the receptors,[78] can constitute starting points to develop or modify therapies and these same data can be used to further validate laboratory researches and clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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