Cinnarizine - Potential Trigger of the Dopamine Supersensitivity Psychosis in Patients with Paranoid Schizophrenia

Particular neurobiochemical model

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Supersensitivity psychosis is a subdiagnosed clinical reality. This entity, however, is insufficiently elucidated from the point of view of the neurobiochemical mechanisms involved in the pathogenesis. The combination of an antipsychotic with a high D2 receptor blocking capacity and a neuroleptic-like substance such as cinnarizine trigger the dopaminergic hypersensitivity mechanisms. This stimulates the sensitivity for dopamine in the prefrontal cortex, ameliorating the negative and cognitive symptoms at the thalamic level, remodeling sensory integration and decreasing tinnitus, as well as in the cerebral tonsil, consequently decreasing the risk of antisocial behavior.

Keywords: cinnarizine, dopamine, supersensitivity psychosis, antipsychotics

Cinnarizine is a piperazine derivative of the chemical formula 1- (Diphenylmethyl) -4- (3-phenyl-2-propenyl) piperazine. [1] Piperazines, together with piperidines, are part of the phenothiazines class. Structural differences arise from the substitution of hydrogen atoms attached to carbon C-2 and N-10 nitrogen, with different chemical structures. [2, 3]

Phenothiazines are characterized by a chemical structure of the tricyclic type, most of the molecules being classified as first-generation antipsychotics (neuroleptics); the most known representatives are trifluoperazine and fluphenazine. Unlike molecules in the neuroleptic class, cinnarizine improves brain circulation for conditions associated with vertiginous symptoms or tinnitus. Cinnarizine has the following pharmacological actions related to its chemical structure:

1. The effect of blocking D2 receptors predominantly at the level of nigro-striatal, mesencephalic and mesolimbic structures. 2. Calcium channel blocking effect, which modifies the reactivity of the electrical synapse in the dopamine circuits and potentiates dopamine deficiency in the basal ganglia, emergence zones (black and ventral ventricular area) and midbrain, translated into decrease of the positive symptoms in schizophrenia, reinforcing the neuroleptic-like effect.

Both mechanisms act synergistically, causing dopamine levels to decrease both in the presynaptic pole and in the postsynaptic pole. Since the 1990s, psychotic symptomatology has been amplified in patients with paranoid schizophrenia and long-term antipsychotic treatment, a phenomenon explained by D2 dopamine receptor blocking mechanisms. In this type of psychosis, called dopaminergic supersensitivity psychosis, the major trigger factors are little known, even if the diagnostic criteria are well structured. [4] 3. Histamine H1 receptor blocking effect act in correlation with dopaminergic receptor hypersensitivity. H1 blockers increase the level of dopamine in the nucleus accumbens and striatum, in the case of schizophrenia being a mechanism that can trigger supersensitivity psychosis. [5] Excessive use of substances blocking H1 receptors lower neurogenesis in the subventricular area, leading to cognitive dysfunction and negative symptoms in schizophrenia [6].

H1 blockers induce obesity by activating adenosine monophosphate kinase (AMPK) at the level of the hypothalamus. [7] Thus, antipsychotics that have the ability to block H1 receptors with rapid weight gain due to their chemical structure predict the risk for supersensitivity psychosis. [8]

Supersensitivity psychosis can be considered a significant clinical marker for the risk of developing tardive dyskinesia. [4] Substances that induce extrapyramidal symptoms with neuroleptic-like effects may be neuroleptic or non-neuroleptic [9, 10].

Experimental part

We performed a retrospective observational study a group of 36 patients over 45 years, 20 males and 16 women.

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These patients were hospitalized with the diagnosis of paranoid schizophrenia in the psychiatric clinic of the Clinical Neuropsychiatry Hospital in Craiova between 2011-2015.

Inclusion criteria: acute psychotic episode of paranoid schizophrenia, over 45 years of age, disease progression for more than 10 years, constant antipsychotic therapy with significant D2 blocking capacity (haloperidol, risperidone), history of extrapyramidal symptoms, treatment with anticholinergic (tri-hexi-phenidyl) and antiparkinson drugs had been administered for at least 6 months, good compliance and adherence to treatment, lack of acute psychotic symptoms in the last 3 years, presence of tinnitus during the last 6 months for which treatment with cinnarizine has been recommended by a specialist (neurologist, ear, nose, throat - ENT)

Exclusion criteria: The presence of acute or chronic somatic and/or cerebral diseases: Type I and II diabetes mellitus, transient ischemic stroke or history of stroke, major cranial trauma, neoplastic disease, HIV infection, epilepsy, antipsychotic therapy long-acting or electro-convulsive therapy. Other ENT pathology was excluded.

All patients or their caregivers have signed informed consent and personal data has been used in accordance with applicable regulations. The study was conducted with the approval of the Ethics Commission of the Clinical Neuropsychiatry Hospital in Craiova.

The statistical processing of demographic data (age, residence, schooling, work, marital status) and the number of relapses relative to the sex of patients is shown in Table I.

Patients followed long-term (over 5 years) long-term treatment with antipsychotics with significant D2 blocking capacity (haloperidol, risperidone). Patients were treated concomitantly with cinnarizine, prior to the current admission, for a duration longer than 4 weeks due to the occurrence of tinnitus. All patients had extrapyramidal phenomena for which they received trihexifenidyl over a period of at least 6 months. The overall evolution over the last 3 years, assessed retrospectively, anamnestically, did not reveal acute psychotic events, the symptomatology being dominated by negative phenomenology and minimal cognitive dysfunction evaluated at the time of admission using the MMSE scale (the scores for the entire group ranged between 21-27 points) (fig. 1).

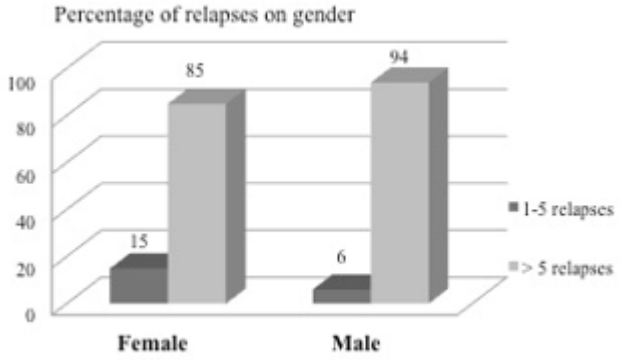

Fig.1 The analysis of relapses on gender

The psychotic symptom for which they were admitted occurred after at least 21 days of treatment with cinnarizine 25 mg, 3 tablets / day, with positive symptoms and short confusional episodes.

Results and discussions

Following the analysis of the clinical cases included in the study, several features of the hypersensitivity mechanisms of the dopaminergic circuits are presented. Paranoid schizophrenia is the consequence of dopaminergic hyperactivity, [11] its association with positive symptoms was demonstrated. Several studies have shown the induction of psychotic phenomenology on experimental bases by the use of dopamine agonists (amphetamines, apomorphines) [12,13]. The effect of schizophrenia-like psychosis has been suspended by administration of substances that block D2 receptors from the previously mentioned dopaminergic areas [14,15].

Positive symptomatology was subsequently correlated with increased activity of dopaminergic level in the mesencephalic and cortical areas. The negative and dyscognitive symptoms were associated with the decrease in dopaminergic transmission from the cerebral cortex, predominantly in the prefrontal cerebral cortex. [16,17]

The limits of first-generation antipsychotic therapy have been accepted due to limited action only on positive symptoms as well as the increase in dopamine deficiency. Recognition of these limits has led fundamental pharmacological research to find new molecules that have been called atypical or second-generation antipsychotics. These molecules act on the dopamine / serotonin balance and the established criteria for defining these

		Male		Female	
Gender		20		16	
Age	45-60	15	75%	14	88%
	over 60 ani	5	25%	2	13%
Background	urban	12	60%	9	56%
	rural	8	40%	7	44%
Education	elementary	8	40%	7	44%
	high school	9	45%	8	50%
	higher	3	15%	1	6%
Workplace	stable	4	20%	4	25%
	none	6	30%	7	44%
	retired	10	50%	5	31%
Marital status	married	8	40%	7	44%
	single	5	25%	3	19%
	divorced / widowed	7	35%	6	38%

Table I
DEMOGRAPHIC DATA OF THE ANALYZED GROUP RELATED TO THE SEX OF THE PATIENTS

antipsychotics are: efficacy on positive and negative symptoms, minimal extrapyramidal effects, do not induce high prolactin levels and there is a minimal risk for late dyskinesia [18].

Clinical experience has shown that approximately 30% of patients with schizophrenia, during evolution have a lower response to antipsychotic drugs, by setting up resistance therapy. [19] For these reasons, associations between two or more antipsychotics have been used [20], but the results are inconstant and have caused paradoxical effects such as the psychosis rebound, which has led to the definition of psychotic sub-entities (supersensitivity psychosis, rebound psychosis) [21,22].

In our study, we present the potential for the development of a supersensitivity psychosis by associating some of the drugs that are little known in clinical medical practice, which are part of the neuroleptic-like drugs category.

Dopamine hypersensitivity psychosis is based on the effects of hypersensitivity of D2 receptors after prolonged antipsychotic treatments, which at the time of the onset of psychosis receive agonists or partial dopamine agonist. [10]

The occurrence of psychotic flared up in schizophrenic patients, in the group analyzed by us, 3 weeks after the administration of cinnarizine for tinnitus has suggested the presence of other pharmacological mechanisms that may be involved in the psychosocial hypersensitivity. Cinnarizine blocks calcium ion channels and acts as a neuroleptic-like substance by blocking D2 variants of receptors (D3 receptors).

Pharmacological clinical stages of the dopaminergic model

Three pharmaco-clinical stages are distinguished in the model we propose. In patients with long-term paranoid schizophrenia and predominantly antipsychotic treatment with high D2 receptor blockade, the following variations occur compared to the normal status of dopamine system involvement in the pathogenesis of schizophrenia.

A. In normal conditions, dopamine is secreted in excess at the level of the emerging secretion and dopamine release system, represented by ventral tegmental area and substantia nigra, dopaminergic structures dominated by classical D2 receptors (fig. 2).

Accumbens nucleus is the main intersection of dopaminergic pathways on their way to the cerebral cortex. [23] The accumbens nucleus is predominantly populated by D3 receptors, D2 variant receptors. The accumbens nucleus has multiple connections and the most important from our point of view is the connection with the cerebral

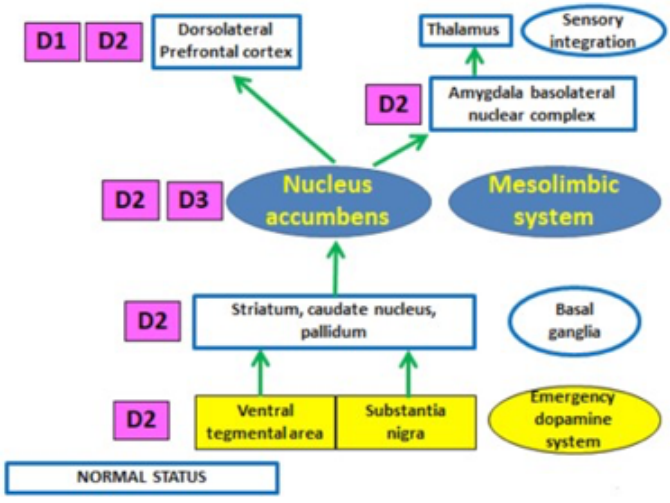

Fig. 2. Dopaminergic system in stable conditions

amygdala, which is a major area of the limbic system that controls behavior, emotivity and decisional involvement.

A particular amygdalar structure has been described, called basolateral nuclear complex in which D2 receptors dominate which can be blocked by high-potency antipsychotics for these receptors, involving oxidative stress cascade [24,25]. Usually, there is a numerical and qualitative balance in the prefrontal cortex between D1 receptors (D1-D5) and D2 receptors (D2, D3, D4) [26].

Furthermore, in this area there is also an interdependence between the quantities of extracellular ionic calcium and dopamine so that the D1 and D2 receptors are able to regulate the number of ion channels in dopamine neuronal calcium systems. The calcium-controlled electrical synapse regulates dopamine auto receptors predominantly at this level [27-29].

B. During chronic long-term therapy with antipsychotics with a high potential for D2 receptor blockade, the decrease in dopamine level in the basal ganglia causes extrapyramidal phenomena (fig. 3). In the accumbens nucleus, unbalancing the ratio between D2 and D3 receptors causes depression and addictive tendencies, making a real reward disorder pathology[30]. Simultaneously, the same imbalance amplifies the disconnectivity of cerebral amygdale, especially at the level of the basolateral nuclear complex, favoring the emergence of social behavioral disorders manifested through aggression, violence, suicide [31-33]. In animals it has been described an aberrant type of a global talamo-cortical connection that could represent the neurobiological model for the appearance of tinnitus in patients with schizophrenia [34,35] .

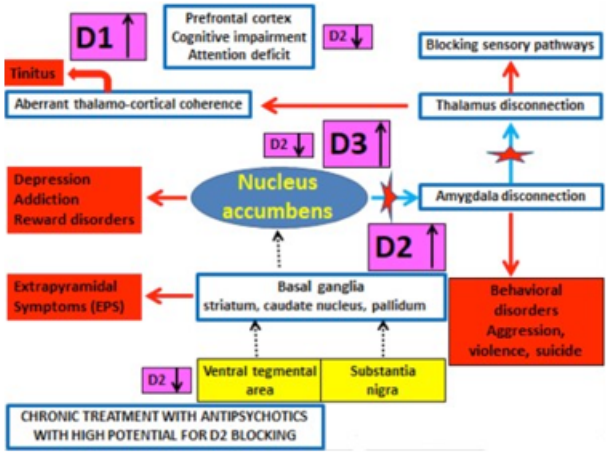

Fig. 3. The dopaminergic system during chronic long-term therapy with antipsychotics that block D2 receptors

Tinnitus can be a prediction factor of a state of neuronal hyperactivity that is in standby conditions. Thus, non-pulsatile tinnitus may be an indirect marker of the risk of disease relapse, while pulsatile tinnitus indicates a stroke risk [36-38].

C. Treatment associated with a neuroleptic-like (cinnarizine) blocks D2 and D3 receptors as well as calcium ion channels causes an increase in dopamine release from basal structures following D1 receptor activation in the prefrontal cortex (fig. 4) [39-41]. Cinnarizine increases the activity of PLC-β1 phospholipase in the prefrontal cortex using the extracellular calcium. This activity may be a marker in the appreciation of clinical evolution because it is known that the PLF-β1 phospholipase deficiency in the prefrontal cortex is a neurobiochemical / enzymatic marker in post-mortem assessment [43, 44].

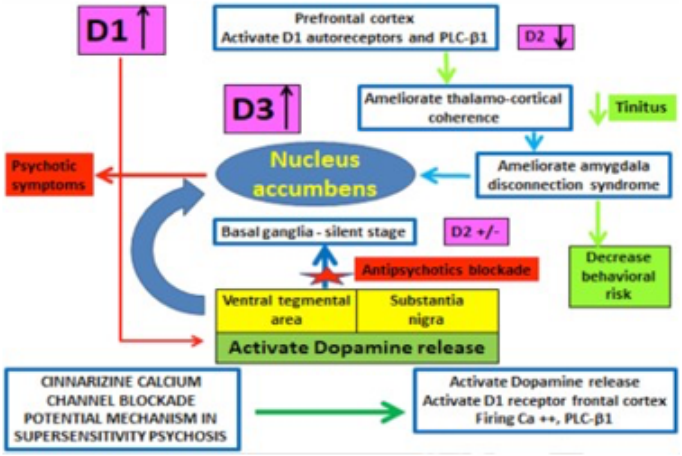

Fig. 4. The dopaminergic system during chronic long-term therapy with antipsychotics that block D2 receptors

Activation of D1 receptors causes the transmission of activating signals to the dopamine electrical synapses in the ventral tegmental area and substantia nigra, triggering a rapid and massive release of dopamine, greatly amplified by calcium ions [45].

By acting directly on the accumbens nucleus and D3 receptors, dopamine causes an acute psychotic relapse dominated by positive symptoms. This type of relapse may, in our opinion, be framed in an alternative model of dopaminergic supersensitivity psychosis.

Conclusions

Supersensitivity psychosis is a subdiagnosed clinical reality. This entity is, however, insufficiently elucidated regarding the neurobiochemical mechanisms involved in the pathogenesis. The alternative pathogenic model suggested by our research based on clinical data and translational evidence is based on the following arguments:

Increase in D2 receptor number and sensitivity after long-term antipsychotics with D2 blocking capacity and decrease in D1 receptor number and sensitivity, predominantly in the prefrontal cortex.

Increase of extracellular calcium ions level in the post-synaptic area following the long-term depression of electrical potential after the D2 blockade.

The increase in number and sensitivity of D3 receptors in the accumbens nucleus. Thus, the mesocortical level is in a potentially hyperactivity state that cannot be triggered because release of dopamine from emerging levels reaches the accumbens nucleus in only a small amount, whilst being retained in the basal ganglia (dopaminergic seizure), following antipsychotic therapy.

Decrease in extracellular calcium ions level after cinnarizine administration and increase in ionic calcium in postsynaptic neurons.

Triggered mesolimbic dopaminergic hyperactivity is equivalent to exacerbation of positive symptoms in schizophrenia.

The alternative model presented by us may bring clinical benefits and prediction risk factors through clinically markers (non-pulsatile tinnitus, allergic manifestations that predict the risk of supersensitivity psychosis).

The relatively small number of cases requires an expansion of clinical research to find the statistical evidence needed to support the theoretical model. Future research may confirm or disprove our hypotheses, but recognition of alternative pathogenic models can improve prognosis and quality of life in patients with paranoid schizophrenia with a chronic evolution and long-term treatment.

Note: Figures 1, 2, 3 are taken from the postgraduate educational course Aspects of clinical psycho-pharmacology in the treatment of schizophrenia, University of Medicine and Pharmacy of Craiova, 2019, Ileana Marinescu, Puiu Olivian Stovicek, Dragos Marinescu.

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