Therapeutics, Pharmacology and Clinical Toxicology
Vol XIII, Number 1, March 2009
Pages: 9-32

STATE-OF-ART

LONG-LASTING EFFECTS OF ANTIPSYCHOTICS TREATMENT. NEUROBIOLOGICAL MODULATING AND RESETING

V.A. Voicu[1,2], F. Rădulescu[3]

[1.] *Department of Clinical Pharmacology, Toxicology and Psychopharmacology, Faculty of Medicine, University of Medicine and Pharmacy „Carol Davila" Bucharest, Romania.*
[2.] *Medico-Military Scientific Research Center, Bucharest, Romania.*
[3.] *Faculty of Pharmacy, University of Medicine and Pharmacy „Carol Davila" Bucharest, Romania.*

Abstract. The authors make a short presentation of antipsychotics' mechanisms consecutive to the interaction with receptors of the neurotransmission systems, respectively the meso-cortico-limbic dopaminergic system, the serotoninergic, glutamatergic, cholinergic systems and so on. Hence, a brief review is performed by means of the pharmacological proofs of schizophrenia pathogenic theories.
Another of the regarded domains addresses the etio-pathogenic aspects of schizophrenia as background for potential pharmacologic targets – the genetic component and the impact of factors which disrupt the neurodevelopment and / or initiated neurodegeneration processes in favorable contexts.
The authors analyze the effects of antipsychotics correlated on various receptor levels with the complex therapeutic effects on schizophrenia. Existing data show that these effects can either be: 1) the direct consequence of action on receptor or the indirect outcome of counter-regulations determined in other neuromediation systems, or 2) these effects can be relatively immediate (a matter of hours - days) or slowly instated (weeks) or, these effects can not appear at all (resistance to treatment, non-responders etc.). In this regard, two concepts are brought into discussion: the therapeutic effects with immediate onset and definition after 2-3 weeks and the slow effects, sharpened up after around one month and either defined or not after a few months.
Another type of reasonings are also brought into discussion: the slow and late effects of antidepressants, the onset of the addiction phenomenon as a complex neuroadaptive process, and also the experimental and clinical proof that antipsychotics induce complex phenomena on cerebral structures. In fact, in the context of chronic antipsychotic treatment, the brain behave according to the acknowledged rules: it launches short latency, rapid processes with homeostatic destiny, thus initiating a series of other, slower reactions, implying protein and receptor synthesis, synaptic plasticity, neuroplasticity, neurogenesis etc. These processes, which entail changes in the expression of certain genes, are approached as epigenetic phenomena which confer to the organism, on one hand, flexibility and adaptability and, on the other hand, genomic stability. Given this context, the authors deem that there are convincing arguments (either direct or indirect) towards admitting that throughout the interaction antipsychotic – pathogenic psychotic processes, two successive interdependent and correlated phases are envisaged: 1) the pharmacodynamic phase where the active compound determines the known effects consecutive to antagonizing or activating the receptors for which it has affinity and 2) the pharmacotherapeutic phase implying slower, more complex processes.

Acad. Prof. Victor A. Voicu MD, PhD
University of Medicine and Pharmacy „Carol Davila"
8, Floreasca Str., Bucharest, Romania
Phone: +40318.07.04
Email: victor.voicu@yahoo.com

The rapid counter-regulations of the interconnected neurotransmission systems are part of the phenomena which probably initiate slower and more complex reactions entailing compensatory phenomena in a positive or negative sense (up or downregulation) at receptor level, neuromediator synthesis, synaptic connections or even the emergence of new neurons in certain cerebral regions. This second phase will outline the final therapeutic response which will install in weeks, months. In connection with the rearrangement, modulation and resetting between different neurotransmission systems (affected in the schizophrenia context), on the basis of the presented epigenetic processes, we might either report or not an individual therapeutic effect as hinted end-point.
Keywords: antipsychotics, treatment, neurotransmission

Introduction

In this paper we begin a short synthesis of data on schizophrenia pathogenic mechanisms. We shall at least bring to attention major alterings in dopaminergic, serotoninergic, glutamatergic, gabaergic, cholinergic (and so on) neurotransmissions stressing the significant alterings of their quality/quantity ratios in the involved areas (mesocortico-limbic).

Starting from this aspect, based on literature and personal data, we will try to build a concept of chronic antipsychotic treatment consequences at level of target systems and their interrelations with other central neurotransmitters systems.

The existing data in this specific field of interest supports the belief that the altering of dopaminergic neurotransmission, among direct consequences on the function of the frontal cortex and the limbic system, also convey significant consequences on the interrelations with other major neurotransmission systems. Provided we admit that the altering of dopaminergic neurotransmission be a primum movens based on the pharmacologic testimony of the significant clinic efficiency of D2 receptor blocking („transient D2 R occupancy is sufficient for atypical antipsychotic effect" – see Kapur S. and Seeman P., 2001), we might either consider

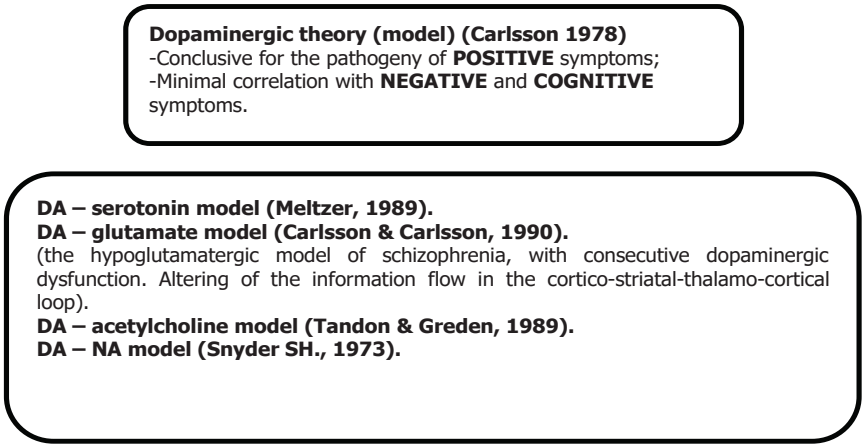

Figure 1. – Pathogenic mechanisms of schizophrenia in terms of neuromediators

Note: *Disruption of DA functions is essential and dominant in schizophrenia, but the dopaminegic system is intricately interconnected to other neuromediation systems.*
There is a suggestion for imbalance of DA and other neurotransmission systems involved in behavior and cognition, sketching a complex pathogeny.

We emphasize the fact that the dopaminergic theory is leading among other pathogenic theories for schizophrenia. The dopaminergic theory of schizophrenia has been perfected through the knowledge of alterings in the dopaminergic, mesocortical, mesostriatum, mesolimbic functions and of their correlation with other neurotransmission systems (**Figure. 1**).

that other described changes are consecutive to the altering in the dopaminergic link, or that these alterings can coexist and persist and they can set off the complex disease only by reaching a quality/quantity-related critical mass. (B.Woods, 1998).

During the past half century, antipsychotics (either typical or atypical) have provided for an important progress both in the comprehension of

the neurotransmission mechanisms and in the better understanding of the pathological mechanisms of schizophrenia. **Table I** presents for comparison the particular affinities of certain illustrative antipsychotics for cerebral receptors. Of course, pharmacologists have reason enough to ask to what extent these antipsychotics bear similarities and/or differences and which is their relevance? (J.Arnt et al, 1998; Davis JM and Chen N, 2005)

pharmacological action on the neuromediation systems – altering of the ratios between system components – repositioning and modulation – resetting and stabilizing.

In this respect we support these ideas by bringing a neurobiological phenomenon into the spotlight. This phenomenon is documented in drug addiction which in certain conditions can have consequences over the entire life span of the person, due to com-

Compound	Receptor mechanism
Amisulpirid	D2 and D3 antagonist
Aripiprazole	Intense antagonist / Partial agonist — D2 R (intense affinity) Partial 5HT1A R agonist 5HT2A R antagonist
Clozapine	Relatively weak antagonist for D2 R Agonist/antagonist to Muscarinic R Partial agonist to 5HT1A R
Olanzapine	Antagonist for D2 R, Muscarinic R, 5HT2A R and 2C R, H1 R
Risperidone	Intense antagonism for D2 R, 5HT2A R, α1
Haloperidol	Intense antagonism for D2 R Weak antagonist for 5HT2A R (in molecular terms – 3 times higher affinity that that of quetiapine

Table. I – Receptor mechanisms involved in the effect of major atypical antipsychotics and haloperidol (adapted and modified after GP. Reinolds, 2004 and PF. Buckley, 2007)

The sensible deduction is the complexity of multireceptor affinity on one hand and on the other hand, the quantity and quality differences in the interaction of different antipsychotics with the respective receptors.

New approaches are being fathomed based on the fact that all antipsychotics are (or can be) inverse agonists to the D2 receptors! (Kenakin T., 2001, Robert D. and Strange Ph., 2005; Hill SJ., 2006).

Certain antipsychotics are agonists/antagonists to D2 dopaminergic receptors, correlated with their (populational heterogenic) functional state (Kenakin T., 2001). This all suggests that the interaction of antipsychotics with cerebral neurotransmission systems is far from static, their interaction with the receptors, bearing as results the alteration of respective receptor population and of interrelations with other systems, thus leading to a dynamic modulation process and lastly to system resetting (Voicu VA., 2005). If stabilizing were to be mentioned (Carlsson A. et al, 1999; Stahl S., 2001; McQuade RD. et al, 2002), this complex phenomenon could be in our opinion relevant in the subsequent cycle: complex plex and stable altering of the cerebral structures involved (Volkow ND. et al, 2004; Kalivas PW and O'Brien C., 2008).

Abuse drugs present intense interaction with cerebral neural circuits, altering the motivational and decisional pathways, thus generating a clinic framework of compulsive behavior destined and oriented towards obtaining the drug. Addiction is considered a pathology characterized by neuroplasticity induced by the drug abuse, together with hypoactivity to normal motivational stimuli, hypofrontality (diminished prefrontal cortex activity) and lowering of the level of D2 striate receptors, associated to alterings in the glutamatergic and gabaergic pathways. Not less relevant are the neurobiological mechanisms of the placebo effect on the brain.

Based on the available data, we will furtheron undertake demonstrating the idea that chronic administration of antipsychotics (as well as that of other psychotropic drugs) does not only entail short-term pharmacodynamic consequences (correlated with the dose and the rhythm of administration)

but it does involve complex, long-term processes, synaptic plasticity, neuroplasticity, neurogenesis (and so on) included.

Obviously, things aren't by far as simple even if the occupancy of the D2 receptors is indispensable to any analysis. Yet, experimental and clinic facts such as the relatively low affinity of clozapine for D2 receptors and the prevalence of 5HT2A receptor affinity significantly perturb this concept (see also Myamoto S. et al, 2005). It is difficult not to consider the consequences of 5HT2A R block and of agonist effect on 5HT1A R explaining, at least in part, the clinical effects of some antipsychotics, of which we mention clozapine. How much more so it is considered that 5HT2A R affinity is neither necessary nor sufficient.

The development of the dopamine – serotonin antagonism theory (Meltzer HY. et al, 1989) has become a criterion for deeming the atypicality. The concept significantly fills out the outline of scientific acquisition in the given field of research.

Certain characteristics of antipsychotics – cerebral receptors interaction

Typical and atypical antipsychotics are pharmacologically characterized by their multi-receptor affinity, basically interacting with roughly 16-18 receptors (see **Table II**) among which we could mention dopaminergic, serotoninergic, cholinergic – muscarinic, adrenergic, histaminergic receptors (their subtypes included). Antipsychotics are structurally, pharmacologically and therapeutically non-homogenous compounds (Meltzer HY. et al, 1989).

An overview according to Arranz MI. and de Leon J. (2007) underlines the fact that antipsychotics have a complex multitarget pharmacologic profile without an obvious action mechanism, at least to the extent of our limited current understanding. Still, antipsychotics make for a 50% clinic efficacy in the treatment of schizophrenia, which compels us to admit to a solid mechanism of action.

The effects on dopaminergic receptors are usually antagonistic, the affinity towards the D2 receptor being crucial for the antipsychotic outcome. This characteristic – the D2 receptor antagonism – is thought to be „necessary and sufficient" for the antipsychotic effect (Kapur S and Seeman P., 2001). At a focused analysis of the interaction, we notice that it can either be antagonistic to D2 receptors, as for D1, D3, D4 receptors, with high affinity for D2 R (Ki=0,34 nM for aripiprazole or 3 nM for

Receptor type	Type of action	Clinic consequences
D2 R	Antagonism	Decrease in positive symptoms Extrapyramidal effects Deficit syndrome induced by the antipsychotic (increase of negative symptoms and cognition)
D2 R	Antagonism / partial agonism	Decrease in positive symptoms Decrease in negative symptoms Ameliorated cognition Lowered or absent extrapyramidal effects
5HT1A R	Partial agonism ↑ Dopamine	Amelioration of negative, cognitive symptoms Decrease of anxiety Decrease of depressant symptoms Decrease of extrapyramidal effects
5HT2A R	Antagonism	Lowered of absent extrapyramidal effects
Muscarinic R	Antagonism	Amelioration of negative symptoms Antagonizing of extrapyramidal effects Anticholinergic side effects
Muscarinic R	Agonism	Amelioration of cognition and psychotic symptoms
5HT2C R	Antagonism	Diminishing of general disease symptomatology
H1 R	Antagonism	Weight gain
		Weight gain

Table. II – Therapeutic and adverse effects of antipsychotics consecutive to cerebral receptors interaction

risperidone) or agonistic – antagonistic (concept which regards the receptors as a non-homogenous population with different functional states) or even further, basically all antipsychotics are inverse agonists (Robert D. and Strange Ph., 2005).

The inverse agonist suppresses the receptors' basal, constitutive activity (Kenakin T., 2001), independent to the agonist's effect, it converts the receptor to inactive state. In this manner, the antipsychotics can act as agonists, with effects opposed to those of DA, increasing the DA release – as alternative to the blocking effect on D2 receptors! Another consequence is the positive numeric compensation (upregulation) of D2 receptors, essential to the antipsychotic outcome.

The affinity ranking for D2 receptors (excepting aripiprazole which is an agonist/antagonist) starting from the highest and ending with the lowest affinity: risperidone > ziprasidone > olanzapine > clozapine > quetiapine.

Clozapine for example has a higher affinity for D1 and D4 R than that for D2 R!

Opposed to typical antipsychotics, the atypical ones (except aripiprazole and amisulpiride), have a considerably higher affinity as antagonists for 5HT2A R than for D2 R.

Atypical antipsychotics are antagonists at the level of 5HT2C R and partial agonists for 5HT1A R. It defines "atypicality" as particularly dissimilar characteristics for variable atypical antipsychotics – certain authors evaluating such characteristics through either chemical of solely clinical criteria (Richardson E., 1999). We record, with consequences mainly adverse effect-related, the antihistaminic actions, α1, α2 blocking adrenergic and antimuscarinic (M1) effects. There already is proof of the agonist cholinergic effects of clozapine (in particular those of the desmetil-clozapine metabolite) with important consequences on the cognitive function.

Within these complex pharmacodynamic effects with virtually immediate onset, we notice that the therapeutic effects are slowly instated, most authors estimating a minimum of 3 weeks to 2-3 months before noticing the clinical changes. A noteworthy number of patients manifest lack of response or intolerable side effects.

Thus spawns the unavoidable question: why the temporal dissociation between immediate pharmacodynamic effects (consequent to receptor occupancy) and late (slowly induced) therapeutic effects? For a different category of psychopharmacologic agents (antidepressants) the concept of a slow instating therapeutic effect seems less argued upon (Duman R. et al, 2001; Frazer A., Benmansour S., 2002).

Even militants for the relatively immediate therapeutic antipsychotic effect which progressively increases from the first week and gains sharpness within the next 3 treatment weeks admit that a certain 20-30% of the patients are non-responsive or partially-responsive (Kapur S. et al, 2005).

Furtheron, based on the available data in psychopharmacology literature, we will try to establish a viewpoint in accordance to various neurobiology related scientific information.

Neuropathologic alterings in schizophrenia. Premises

The proof of neuropathologic alterings in schizophrenia is relevant, dating roughly 100 years back (Wernike CS, 1906, quoted by Stephan K. et al., 2006). Remarkable progress in this field of work has been attained through imagistic methods which demonstrate the existence of quantitative structural alterings ever since the first episode. The quoted author reveals the fact that, on neuropathologic level, the proof is mostly on the negative side: first off, there are no degenerative lesions despite the prominent cognitive deficit, secondly there are no gliosis processes (proliferation of astrocytes) to emphasize inflammatory and degenerative phenomena (Woods BT., 1998; Harrison PJ., 2005). Moreover, an increase in the incidence of Alzheimer disease cannot be observed in schizophrenics.

The obvious aspects are defined by low cerebral weight, smaller neurons, and a downward slope for synaptic and dendritic markers. The more controversial aspects quoted are: neural density altering, smaller dimension thalamus, hemispheric asymmetry of the pathology.

A series of data presented by various authors stress that schizophrenia is a synapse disease, respectively a connectivity dysfunction in the cerebral areas involved (Harrison P., 1999; Mirnics K. et al, 2001; Gordon Frankle W. et al, 2003; Friston KJ., 2005).

The affliction of synaptic transmission can either be local (enclosed area) or detached, as are cortico-cortical, interhemispheric and cortico-thalamic connections.

These facts concur towards schizophrenia's etiopathogenic theory as much rather a process of neurodevelopment than as neurodegenerative process. Judiciously, the facts suggest a phenomenon

with early emergence in the evolution of the brain. The symptoms evidently manifest much later, detail which needs further explanation. What is interesting is that a series of proteins coded by genes possibly involved in schizophrenia pathology have functions on synaptic level (Gogos JA. and Gerber DJ., 2006; Harrison PJ. and Weinberger DR., 2005).

For example, the altering of dopaminergic transmission can be considered an illustration of synaptic dysfunction with complex consequences such as the negative, positive and cognitive symptomatology in schizophrenia.

Reasoning in favor of synaptic dysfunction (Gordon Franke W. et al, 2003) as background for pathogenic mechanisms in schizophrenia is extremely suggestive for the intricacy of the antipsychotic therapy resetting effects on these conditions.

Name	Association with schizophrenia *)	Biological plausibility (in vivo or in vitro expression)
COMT	++++	++++
Dysbindin	+++++	++
Neuregulin 1	+++++	+++
RGS4 regulator	+++	++++
DISC1	+++	++
Glutamate - 3 metabotropic receptor	+++	++++
G-72	+++	++
D-aminoxidase	++	++++

Table. III – Susceptible schizophrenia candidate genes (modified after PJ. Harrison and DR. Weinberger)

The potential functions of the proteins coded by the candidate genes address glutamatergic transmission (proline metabolism), release of glutamate (lysosome biogenesis), neuronal development and survival, synaptic function, pinpointing of membrane receptors and signal transduction, synaptic architecture and plasticity, neurotransmitter reuptake and depositing, GABA mediated transmission, dopamine metabolism, regulation of the extracellular dopamine level in the prefrontal cortex, regulation of the GTPase activator which modulates the signal transduction to dopamine, glutamate or muscarinic receptors etc.

For instance, dopamine diminishes the excitatory transmission between (glutamatergic excitatory) pyramidal neurons through action on presynaptic D1 R. This indicates that the glutamatergic hypofunction can be generated via D1 R activation.

Major dysfunctions correlate with an excess in dopaminergic D2 R associated to a glutamatergic transmission deficit. We have found experimental and clinical proof on the psychotogene consequences of a dopaminergic excess induced by am-

Gene	Function
COMT	Metabolism (oxidation) of dopamine; Regulation of extracellular dopamine in prefrontal cortex.
Neuregulin 1	Widespread involvement in neural development, survival and synaptic function.
RGS4	GTPase activator which modulated the signal transduction through dopamine, metabotrope glutamatergic and muscarinic receptors.
DISC1	Multifunctional, involved in cytoskeletal and centromere functions, in membrane location of receptors and signal transduction.
Glutamate - 3 metabotropic receptor	Receptor synthesis and glutamatergic transmission.
G-72	Potential modulation of D-aminoxidase and, indirectly, glutamate-mediated signaling.

Table. IV – Potential function of the schizophrenia candidate genes (modified after Gogos and Gerber, 2006

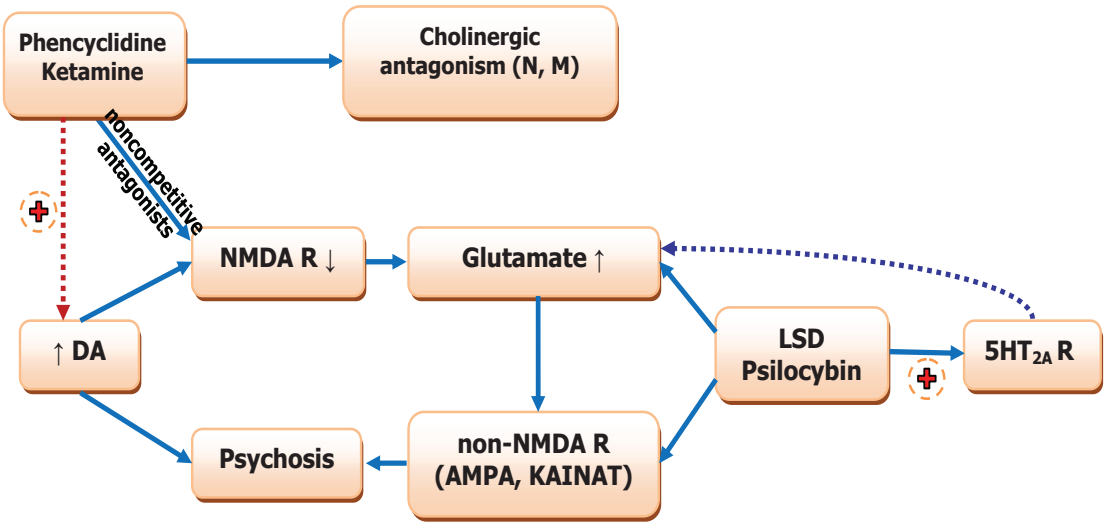

Figure. 2 – Glutamatergic– dopaminergic mechanisms in chemical psychosis

phetamine administration and also on the psychotic effects of non-competitive NMDA R antagonists (phencyclidine or ketamine). Apparently, intense dopaminergic activity is under inhibitory control from NMDA R.

The functional deficit in NMDA R generates a shortfall in the control of dopaminergic activity under stress. The dopaminergic excess supplementary inhibits the NMDA mediated activity in cortical and limbic areas and the connection to the GABA neurons from the neuronal striatum. A vicious circle of deficit is thus created and enhanced.

The abnormal connections seen in schizophrenia consecutive to genetic and environmental congregating factors are predominant in the prefrontal cortex (as execution system) and in the connections to the limbic system, striatum and thalamus. The impact of these synaptic dysfunctions on the complex neuroendocrine puberty and postpuberty events generate an aggression and clinical relevance of the imbalances between excitatory and inhibitory neuromediation on a dopaminergic dysfunction background.

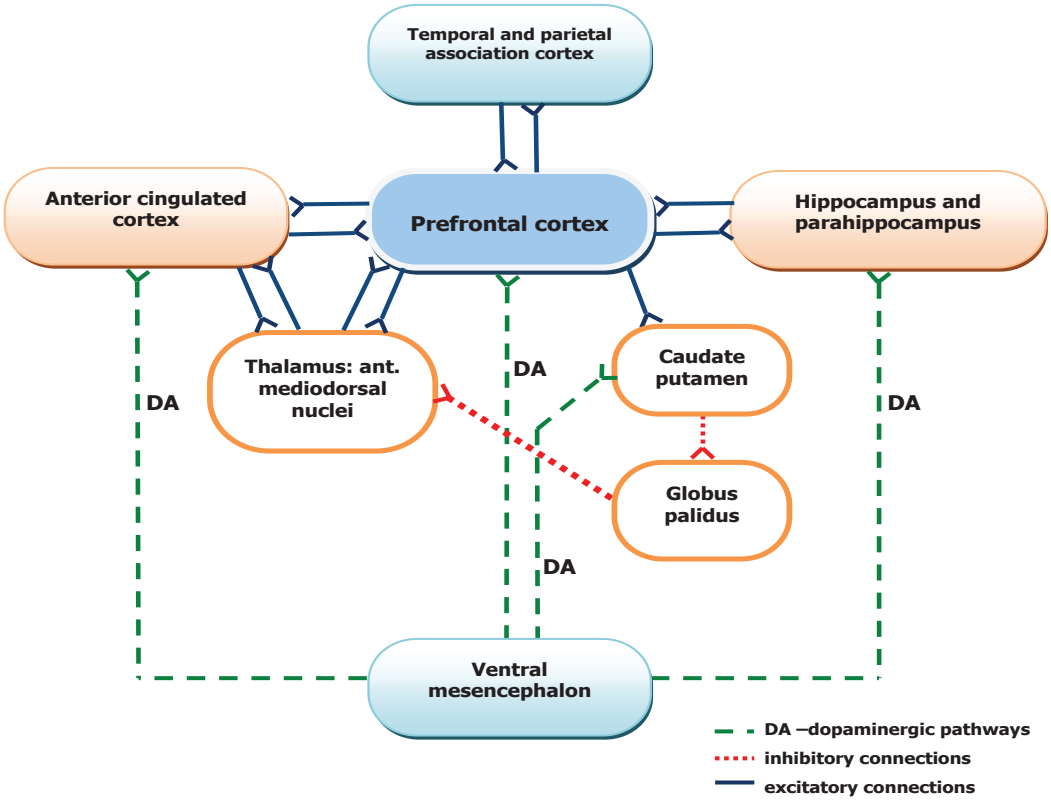

Figure. 3 – Cerebral areas involve in schizophrenia (modified after Lewis DA and Lieberman JA., 2000)

Regarding the approach of the synaptic dysconnectivity theory (Stephen KE. et al, 2006), starts on Friston KJ's hypothesis (1996, 2005) and proceeds to reveal the fact that the altering of nervous system connections leads to the loss of control of the synaptic plasticity which manifests by means of **abnormal central nervous integration**.

Pharmacologic evidences on normal individuals prove that, in a physiologic context, the psychodysleptic compounds can induce schizophrenia-like symptoms, which basically are **completely reversible**, which is obviously not the case with schizophrenia. Genetic studies mention alterings in the function of certain genes which code for proteins involved in synaptic plasticity as a major adaptation phenomenon of the **dynamic integrative connectivity** correlated with the environmental conditions, with learning, exercise etc. Harrison P.J. and Weinberger D.R. (2005) identify 7-8 candidate genes for the pathogeny of schizophrenia out of which 6 are highly linked to NMDA R function and neurotransmission modulation.

Despite all progress in the field of structural and nonstructural altering identification for schizophrenia, this disease as a whole has no definite neuropathologic diagnosis based on univocal, pathognomonic recognition of a certain type of lesions in the involved cerebral areas (Harrison P.J. and Weinberger D.R., 2005). That is why it is considered that schizophrenia seems to consist of altering in the neuronal microcircuits, expressed in the dendritic and axonal connections and in the associated glial elements. These aspects plead for the concept of dysconnectivity consecutive to synaptic disorders (Gordon Frankle W. et al, 2003; Friston KJ. et al, 2005; Stephan KE. et al, 2006; Ross CA. et al, 2006; Suzuki T. et al, 2001; Lledo PM. et al, 2006).

Therefore, the synaptic pathology is only partially morphologic (visible in electron microscopy), the rest being manifest at molecular level and consisting of altering of the synaptic machine's composition, activity and plasticity (Harrison P.J. and Weinberger D.R., 2005).

Studies on twins show that schizophrenia is a predominantly genetic disease, with hereditary risk estimated at 80%. There is no focus on a certain single gene, on the contrary, the polygenic pattern is plausible, the effect of multiple genes with additive and multiplying action corroborates well with existing data (Owen MJ. et al, 2004).

The antipsychotics produce complex modifications in the brain

Most authors admit that the antipsychotic effect is slowly induced and can be of relevance within the first 2-4 weeks. The scientific world is preoccupied by biomarkers for the prediction of both the antipsychotic effect and of the adverse effects.

Actual case studies reveal the absence of direct correlation between the blocking effect on D2 R and the specific therapeutic effect. We notice the necessity of demarcation between the onset of the antipsychotic's effects and the needed time for specific therapeutic effect (Agid O. et al, 2003).

These authors, based on metaanalysis, support the hypothesis that the therapeutic effect commences upon reaching the therapeutic concentration level of the antipsychotic.

Thus, the highest rate of therapeutic response kicks off within the first week, process which is considered a guideline for prediction of the individual efficacy of the respective drug. The authors consider that, as with the hypothesis on the early onset of antipsychotic effect for a certain dose and in a certain patient, the required observation span is 2 weeks.

In the similarly approached context, Frazer A. and Benmansour S. (2002) underline the wide acceptance of the fact that the effects of antidepressants are set off after a lag period of 2-3 weeks with slow maximal or optimal effect after 6 – 12 weeks.

The authors admit effects on synaptic functions with neuroplasticity-generating intracellular consequences, alterings potentially involved in the prophylactic effect of antidepressants (compared to the recurrence of the depressive disease).

Other important elements in the same context are disclosed by Taucher J. et al. (2002) who address the dissociation of plasma level antipsychotic kinetics from cerebral kinetics. Thus olanzapine and risperidone have plasmatic half lives of 24,2 and 10,3 hours respectively, while the decrease to 50% of cerebral concentration (D2 R occupancy) – needs 72,2 h for olanzapine and 66,6 h for risperidone. The fore-mentioned authors describe a similar discrepancy concerning the plasmatic dynamic versus D2 R occupancy on corticostriate level and 5-HT2A R occupancy.

It is significant that D2 R occupancy may persist up to 15 days after the discontinuing of oral administration of typical antipsychotics (Baron et al., 1989, quoted by Taucher J. et al., 2002).

A potential explanation of this dissociation of the two kinetics could consist on how lipophile the compounds are and which is their preferential distribution in the brain, active metabolite (e.g. 9-hidroxi-risperidone) included. In this last scenario the authors admit to a possible altering of cerebral metabolism for the parent-compound, which would explain the prolongation of receptor occupancy.

Herein, the presence of an extremely high „a priori" concentration in the brain will undoubtedly determine significant long term alterings of the afferent functions (receptor density, synaptic functions, neuroplasticity etc.).

The belief that neurons die during the life of a developing individual and in adults has been dominant and only recently has neurogenesis been revealed as emergence of new neurons under certain circumstances, adults included, in a wide variety of mammal species (Chambers RA. et al., 2004).

This phenomenon of neurogenesis is more apparent in certain areas of the brain, such as the dentate gyrus, hippocampus and olfactive system. Neurogenesis is associated to the increase in cognitive performance, social interaction, antidepressant outcome of specific drugs, effects of electroconvulsive treatment etc.

Neurogenesis in the hippocampus under action of antidepressant drugs explains the specific therapeutic effect, the discontinuing of the cognitive deterioration and the performance increase. Apoptosis and neurogenesis coherently interact towards creating a pattern of neuronal turnover functionally adapted to new informative requirements (Chambers RA. et al., 2004; Paizanis E. et al, 2007).

It is already widely known that the substances that have effect on certain fundamental functions of the organism, especially those involved in the homeostatic regulation and control generate long term effects, their discontinuing bringing about grave „abstinence"-like drawbacks with highly significant risk levels. To that effect, we would mention the chronic β-adrenergic blocking treatment, clonidine treatment, benzodiazepine treatment etc. although in circumstances not correlated with therapeutic destiny, long term drug addiction (drug abuse) generates basically irreversible phenomena with negative impact on the individual destiny (and, of course, on the treatment options).

Hypothetically, the chronic antipsychotic treatment, through similitude and not only, through complex interference with multiple neurotransmission systems, should generate significant and durable changes (alterings) on the targeted cerebral areas.

We shall mention certain experimental theses to that respect.

Kontkanen O. et al (2002) daily administers haloperidol and clozapine for 17 days in rats and after 3 washing periods (2 hours, 24 hours and 6 days respectively) studies gene expression in the cerebral cortex.

The study was performed on functional clusters, respectively on genes for GABA R and correlated with GABA neurotransmission, for glutatergic R and correlated with glutamatergic neurotransmission, for G protein-coupled receptors, for genes involved in the lipid metabolism and correlated with presynaptic tasks. Microarray analysis of the expression of candidate target genes (after administering clozapine in the prefrontal cortex at 1, 6 and 24 hours) revealed a differential expression of the genes involved in presynaptic function. Supplementary assessment of the 35 genes was conducted through in-situ hybridization after acute clozapine intake and/or after clozapine and chronic haloperidol treatments. The acute clozapine administration regulated the expression of chromogranin A, synaptotagmin V and calcineurin.

The chronic administration of clozapine reduces the cortical differential expression of chromogranin A. Chronic haloperidol regulated the mARN expression of the inhibitor of DNA-binding 2 (ID-2) and Rab-12. The authors conclude that chronic treatment with haloperidol and clozapine modulate the expression of genes involved in synaptic function and in regulation of intracellular Ca^{2+} in the cortex.

In a different experimental paper, Andersson C. et al (2002) prove that chronic administration of haloperidol, risperidone, clozapine, olanzapine for 8 months determines a neuroplastic response, respectively an increase in striatum volume by means of typical antipsychotics while atypical antipsychotics differentially modify the basal ganglions. Scheepers FE. et al (2001) show that the decrease of caudate volume is positively correlated with amelioration of positive symptoms, but not of the negative ones.

Andersson et al stress on the hypothesis that chronic antipsychotic treatment produces long term altering of the global cerebral structure, as shown by striatum hypertrophy, with circulatory activation, synapse activation, regeneration and number adjustment on this level.

The increased volume of the caudate nucleus is

correlated with weak neuropsychic performance, deficit syndrome and more severe symptomatology, this same increased volume suggesting an adverse modulation of the effects of antipsychotics (Scheepers FE. et al, 2001; Gur RE. et al, 1998).

On the other hand, Sheepers FE. et al (2001) emphasize that decreased volume of caudate nucleus under clozapine, in patients priorly treated with typical antipsychotics (which increase the caudate nucleus volume) is not connected to treatment response and neither to improvement in late dyskinesia. In the given circumstances, the author considers that the neuropathological abnormalities in schizophrenia are dynamic: these tend to be reversible rather than static or irreversible. Plus, the differential effects of typical antipsychotics as opposed to those of clozapine are correlated with the different D2 R affinity.

A different clinical study allows Scheepers FE. et al (2001) to conclude that the significant decrease in caudate nucleus volume is noticed in patients who respond to clozapine treatment, but not in patients who are non-responsive to clozapine after 52 weeks of treatment. Of course, the following question still stands: does this effect directly correlate with the therapeutic effect of clozapine?

Fatemi SH. et al (2006), builds a theory on the ideas that genes with neuroregulating function can be involved in schizophrenia pathology and that recent studies confirm that genes involved in neurotransmission, signal transduction and glutamate/GABA regulation are differentially adjusted in the brains of individuals with schizophrenia. Chronic olanzapine treatment in rats may alter the expression of certain genes involved in the etiology of schizophrenia and mood disturbance.

After daily administration of olanzapine for 21 days, 31 genes were downregulated, 38 genes were upregulated. These alterings were double compared to those in the control group.

These results target the genes involved in signal transduction, cellular communication, metabolic and energetic pathways, transport, immune response, nucleic acid metabolism and neuronal growth factors.

In particular, olanzapine seems to have the effect of increasing glutamatergic neurotransmission, modulating synaptic plasticity, augmenting the energy production via prefrontal rat cortex glycolytic pathway.

Chen ML. and Chen CH. (2005), referring to risperidone, appreciate that besides the profile of receptor interaction, the compound needs two weeks of treatment before showing a therapeutic effect, the molecular mechanism being less ascertained. The mechanism for the slow induced effect isn't completely elucidated.

It is generally admitted that antipsychotics can affect the expression of certain genes in the brain comporting subsequent altering in the synaptic structure and neurogenesis (also see Hyman SE and Nestler EJ., 1996; ; Konradi C. and Heckers S., 2001). It can easily be assumed that the temporal dynamic of gene expression modifications in the brain corresponds to the dynamic of antipsychotic therapeutic effect instatement (Chen ML. and Chen CH., 2005).

Feher L. et al (2005) study the effects of haloperidol and risperidone on gene expression profile in the rat cortex.

The treatment consisted of 4 weeks of daily administration with prefrontal cortex/fronto-parieto-temporal sample prelevation at 96 hours and at 4 weeks. Among the 8000 examined genes only 36 genes (0,45%) had been altered by haloperidol. At 96 hours haloperidol produced a decrease in the expression of 15 genes, and overexpression of some other 13 genes. At 4 weeks, 9 of the genes were overexpressed and none were underexpressed. Among the overexpressed genes at 4 weeks, we mention: G-protein-binding protein, K^+-channel, relaxin-like factor, endotelin receptor etc.

As for risperidone, after 96 hours, 89 genes were modified, out of which 43 had been induced, and 46 underexpressed. Chronically, their number decreased to 6 and, respectively, 11.

The authors deem that the antipsychotics induce or inhibit the expression of certain genes which are functionally involved in signal transduction, transcription and translation, protein turnover and cellular metabolism. All these factors are involved in neuroplasticity, one of the parameters correlating to glutamatergic transmission activation (subunits of NMDA R and glutamate carriers) (see also Hong JS. et al, 2004).

At dopaminergic level, haloperidol and risperidone act on the subtle regulation of signal transduction pathways, implicitly the two antipsychotics induce neuroplasticity. Effects on the endotelin expression are also mentioned. Endotelin is involved, together with the respective receptors in behavior, neuroendocrine regulation and cardiovascular control.

Huang XF. et al (2007) has experimentally de-

termined the effects of clozapine and haloperidol on 5-HT2A R and 2C R expression in rat brains after 36 days of daily administration.

Clozapine exerts a meaningful effect on 5-HT2A R expression: significant decrease in the hypothalamus, in the limbic system (accumbens nucleus – 65%, hippocampus – 80%), in striatum (68%), cingulated cortex (56%). At 48 hours from the last clozapine intake the 5-HT2A R expression was significantly higher compared to control. As for its effect on 5-HT2C R, clozapine produces the deepest effects in the *substantia nigra* which are still significantly present at 2 and 48 hours from the last administration.

Haloperidol at 2 and 48 hours from the last intake produces significant decrease only in the *substrantia nigra* (42% and 54% respectively). According to available data, clozapine, a highly lipophilic compound, is preferentially distributed to the striatum, cortex, accumbens nucleus, hippocampus and hypothalamus, which according to Huang et al constitutes proof of 5-HT2A R expression altering in the respective areas, subsequent to chronic treatment. It may seem a bit peculiar that, opposed to other blocking agents, the chronic blocking of 5-HT2A R leads to their downregulation, and not their upregulation as is usually characteristic.

The authors consider that the effect of 5-HT2A R expression diminishing might contribute to regularizing their function in the hippocampus (on experimental models, the increase of 5-HT2A R in the hippocampus correlates to anxiety and stress related disorders).

The altering of 5-HT2C R expression under clozapine action is strictly limited to the *substantia nigra*. The 5-HT2C R involvement in the control of mesencephalic dopaminergic neurons is known to exert both a phasic and a tonic modulation on the functions of dopamine.

The lack of effect of haloperidol on the expression of the two receptors is justified by the antipsychotic's low affinity for 5-HT2A R and 2C R compared to clozapine.

Huang XF. et al (2006) scrutinize the effect of olanzapine on 5-HT2A R and 2C R expression in rats' brains after daily administration for 36 days. The authors find that olanzapine decreases the 5-HT2A R expression in the hypothalamus, the limbic system and the striatum (accumbens nucleus, amygdaloidal nucleus).

At 48 hours since treatment discontinuation, the 5-HT2A R expression was increased in most of the inspected areas. The most significant decrease in 5-HT2C R expression was present in the *substantia nigra*. Opposed to the usual effect, the blocking of 5-HT2A R decreases their expression!

Chen ML. and Chen CH. (2007) determine the expression of the genes which code for catabolic enzymes of biogene amines, respectively MAO A, MAO B and COMT in rat frontal cortex, after daily doses of risperidone, for four weeks. Similarly, haloperidol, clozapine or olanzapine have been administrated.

The risperidone treatment significantly increases the expression of MAO B and COMT in rat frontal cortex. Olanzapine also greatly increases the expression of MAO A, MAO B and COMT genes. No similar altering has been observed under haloperidol and clozapine. The authors comment by saying that MAO A mutation correlates to mental retard, dysfunctions of impulse control and violent behavior. MAO gene knock-out mice are aggressive, COMT gene being a noticeable candidate for schizophrenia on 22q chromosome. The risk is correlated with lowered COMT mARN expression in the brain. Basically, the decrease in MAO and COMT genes in the brain can be associated to schizophrenia pathogenesis. The long term increase of MAO A, MAO B and COMT expression under risperidone and olanzapine may signify **restoration of disturbed neurotransmission**, which would account for the clinical effects of atypical antipsychotics.

Antipsychotic induced pharmacodynamic and neuroplastic effects

A possible question might be: is the interaction of antipsychotics with neurotransmitting receptors from meso-cortico-limbics areas associated to exclusively reversible pharmacodynamic effects or to complex long lasting altering in the expression of the genes which control the synthesis of neuronal function components? In an article published ten years back, Eastwood SL. et al (1997) researches the expression of genes involved in neuronal activation and plasticity, with the purpose of contributing to the identification of modifications determined by chronic antipsychotic administration. The authors stress on the need for long term studies since the prolonged, slow alterings in gene expression can contribute to late therapeutic effect, as to secondary effects of antipsychotics.

By studying synaptophysin, a protein used as marker for presynaptic endings, after 16 weeks of haloperidol treatment in rats, an increase in synaptophysin expression was noticed in the dor-

solateral striatum and frontoparietal cortex, yet not in the hippocampus. The authors consider this process as the proof that chronic administration of antipsychotic produces synaptic restructuring in certain neuronal populations from the striatum and cortex, but does not comport sustained altering of neuronal plasticity.

Harrison PJ. (1999) shows that antipsychotics, among their neurochemical effects, also produce altering of the cerebral structure which is considered contributory to the therapeutic or secondary effects of antipsychotics. On the other hand, these treatment-induced alterings may be mistaken for the neuropathology of the psychosis itself. From literature data analysis, the author mentions no proof at all that antipsychotics affect cortical neurons or that they could generate neuropathologic altering of the hippocampus. Yet the author emphasizes the fact that there are certain aspects which signify genesis of new synapses and increase in their turnover. Correlated to anatomic distribution of these synaptic plasticity processes, it can be noticed that almost all ultrastructural alterings after antipsychotic treatment are isolated on the nigro-striatal pathways, with preservation of accumbens nucleus, which suggests the association to D2 receptors blockade (with dopaminergic consecutive hypersensitization) and late dyskinesia induction. Bare note that this process isn't described for clozapine, though certain structural alterings induced by antipsychotics do not differ in individual with or without dyskinesia, respectively with of without dopaminergic hypersensitivity.

The pharmacologic and cellular mechanism orchestrating the neuroleptic effects of antipsychotics are at least partially consecutive to D2 R blocking.

In a data analysis, Konradi C. and Heckers S. (2001) address issues related to the mechanisms of the effects of antipsychotics on brain functions correlated to the delayed therapeutic effect (Hyman SE and Nestler EJ., 1996). Although the D2 R blockage is virtually instantaneous, the therapeutic effects are far from being directly associated to the pharmacodynamic ones, the pharmacologic profile of antipsychotics suggesting more complex action mechanisms.

Dean Ch (2006) discus recent proofs on long-term modification associated with antipsychotic treatment: changes in protein affecting cell survival, impaired of the mitochondrial respiratory chain, increase in DNA fragmentation, injury to dendritic microtubules, increases in dopamine-generated reactive oxygen species, changes in cell morphology and rapid induction of apoptosis.

Neuroplasticity (synaptic plasticity and neurogenesis) in the prefrontal cortex, hippocampus and thalamus, is likely to rank high in endpoint of the treatment of schizophrenia. The quoted authors bring into discussion the effect of haloperidol: the increase of striate volume, accompanied by numeric expansion of neurons. Supplementary, haloperidol produces ultrastructural altering in the striate synaptic morphology: growth in the size of axonal endings, increasing of the number of vesicles per synapse and heightening of the postsynaptic density. The effect of haloperidol is reversible in rats after ceasing treatment. On molecular level, haloperidol influences protein synthesis and phosphorylation, both processes being majorly involved in synaptic remodeling, memory and behavior, correlated with neuroplasticity. Haloperidol influences protein phosphorylation via blocking D2 R, activating adenilate-cyclase and increase of cAMP and activation of protein kinase A which phosphorylates the receptors and the ionic channels, thus modulating the synaptic function.

The effects of haloperidol aren't limited to the striatum, even though those are the most notable, they also reach the prefrontal cortex, the hippocampus and thalamus. Konradi C. and Heckers S. consider that the late effect of antipsychotics and the correlated neuroplasticity suggest that ultrastructural modulation of neuronal circuits is a significant contributor to the proprieties of antipsychotics. The involved structures, such as the limbic and prefrontal cortex show synaptic remapping or altering in gene expression as response to the antipsychotic treatment. Successful treatment of schizophrenia could be envisaged as adequate changes in the already altered synaptic connectivity.

Lieberman JA. et al (2005) conducts an imagistic (MRI) study on normal individuals and on patients during their first episode of psychosis, before and after the administration of haloperidol or olanzapine. He essentially notices that haloperidol significantly diminishes the grey substance, while olanzapine doesn't have that effect. In healthy volunteers there is no change in the grey substance volume. The altering of grey substance volume after haloperidol could stand as sequel to the pathologic progress of schizophrenia which isn't impeded by this antipsychotic, while olanzapine can discontinue the process.

The antipsychotic treatment appears to modify the progressive altering of the neurostructures after the first episode. Liberman JA. et al. (2005) demonstrates that the patients treated with typical antipsychotics show a greater loss of grey substance than those treated with atypical antipsychotics. This aspect is obvious for 52 weeks, starting with treatment week 12. The patients treated with haloperidol lose significantly more grey matter from the cortical area in weeks 12 – 24 compared to the patients on olanzapine. In the prefrontal cortex area there are is no altering in patients under haloperidol treatment, while in patients under olanzapine treatment, a minute yet noteworthy increase of the temporal grey matter is noticed, suggesting that this is not only a neuroprotective process, but possibly even a neurotrophic effect (!). Neurocognitive tests show that in the haloperidol treated patients the amelioration is minor, correlated to the cerebral grey matter loss from the prefrontal and parietal cortex.

Liberman JA. et al. (2005) research the effects of antipsychotics on brain morphology within the first psychotic episode, aspect we have previously mentioned saying that the differential effects of haloperidol and olanzapine on brain morphology are either consecutive to haloperidol toxicity (significant decrease in the grey matter volume), or to the fact that olanzapine has superior therapeutic effects. Authors quotes several other researches which show that antipsychotics might have **effects on neuroplasticity, including synaptic remodulating and neurogenesis** (Konradi C., Hecker S., 2001). The morphologic effects of antipsychotics thus culminate with amelioration of neurocognitive processes, PANSS and negative symptoms (Wang HD., Deutch AY., presentation at 34th Ann. Meet. of Soc. of Neurosci., oct.2004, San Diego).

Harisson P.J. (1999), synthesizing literature data, stressed that antipsychotics, additional to their neurochemical effects, also produce structural effects on brain level. Obviously, through their specific effects, antipsychotics have had a tremendous contribution to the better understanding of schizophrenia's neurochemical mechanisms. Thus, by quoting experimental research (mainly performed on rats) regarding typical antipsychotics, the author emphasizes the fact that these compounds lower the number of neurons in the striatum, increase the striate neuronal sizes, give birth to indirect neurogenesis proof etc. Effects on dopaminergic neurons in the *substantia nigra* or in the cortex have not been noticed. Synaptic altering induced by chronic administration of antipsychotics and studied by means of electronic microscopy is characterized by altering of the synaptic ultrastructure on striate level and of lower intensity on cortical level. Although it is hard to systematize these alterings, the author shows that antipsychotics increase the proportion of symmetric axo-dendritic synapses, suggesting that antipsychotics amend the balance in favor of inhibitory synapses, the axo-spinous synapses being excitatory, glutamatergic synapses. Yet data can be found for justifying that synaptic glutamatergic transmission is increased by antipsychotics (Meshul CK. et al., 1996, quoted by Harrison PJ.). The disadvantage in this research mainly results from the fact it has been performed on rats, prominently with haloperidol.

The ultrastructural alterings produced by antipsychotics (in humans, inclusively – postmortem studies) are indications for synaptic plasticity, together with the shaping of new synapses, phenomenon also described in the increase of afferent stimulation, process with significant functional consequences.

The ultrastructural alterings are obvious in the nigro-striatal area, the caudate and accumbens nuclei.

Konradi C. and Heckers S. (2001) pay attention to neuroplasticity in the context of chronic treatment with antipsychotics. The authors circumstantially show that since neuroplasticity is a process through which the brain adapts to environmental changes, it makes perfect sense to consider that antipsychotics have such effects and that these are lengthy.

The two processes involved in neuroplasticity are synaptic plasticity (remodeling and reinforcement of the neuronal circuits) and neurogenesis. The studied data mostly refer to haloperidol. The authors stress that two circuits are particularly relevant in schizophrenia: the reciprocal connexion hippocampus – cortex and the striatal-palido-thalamo-cortical loops. In these circuits the DA neurotransmission plays a dominant role.

Long term synaptic plasticity is correlated with activity, the brain encoding external and internal events in a space-time model implying large neurons ensembles (Citri and Malenka, 2008). If the activity within such circuits lasts, a long-lasting change in synaptic pattern is produced, with new information storage. In fact, the associative memory is accomplished by presynaptic activity harmonization with postsynaptic discharge.

Pharmacologic manipulation of receptors activ-

ity, of their density, of neurotransmitters synthesis and release, of ion-channels dynamics lead to gene expression changes controlling their synthesis. In relation to duration of exposure, the neuroplasticity phenomenon is more ample and stable comparable with addiction phenomenon, for example (McClung AC. and Nestler EJ., 2008).

Schizophrenia can be conceived as a complex neuroplasticity process, reflecting this entity heterogeneity and variability. Thus, there are identified potential schizophrenia causes, deterioration consequences and processes compensating it, in the sense of CNS homeostasis restoration and, finally, our modality to interpret this phenomenon ensemble. Thus, analysing the resultant, including the factors of which some are princeps, defining the perturbation, others associated neuroplastic phenomena not belonging to disease pathological process (Lewis DA. and Gonzales-Burgos G., 2008).

The schizophrenia symptomatology can be analysed and interpreted more unitary as imbalanced plasticity of neuronal network involved in cognitive and psychomotor perceptual functions (Guterman Y., 2007). An epigenetic model of schizophrenia have heuristic value, giving chance to integrate bigger and more diversified epigenetic data in a new concept (Petronis A. et al, 1999). Moreover there are analysed the proofs on abnormal neurogenesis mechanisms, expression of developmental genes in schizophrenia and influence of some antipsychotics on neurogenesis (5HT1A R agonists produce neurogenesis, olanzapine olso etc.) (Cowen SD., 2007; Toro CT. and Deakin JFW., 2007).

The constant working hypothesis might be: if schizophrenia is a dysfunction of synaptic systematization, **antipsychotic induced neuroplasticity** might be the link for **functional and anatomical reconnection**. There is a series of data which confirm haloperidol-induced neurogenesis in the hippocampus (Cameron and McKay, 1998, quoted by Konradi C. et al, 2003).

Proof of neurogenesis through antidepressants is already renowned (Malberg et al., 2000). Certain data underline the effects of atypical antipsychotics on the expression of some neuronal genes in the afflicted area in the context of schizophrenia.

Konradi C. and Heckers S. (2003) suggest that **the delayed therapeutic effect** of antipsychotics could be explained by the fact that antipsychotics promote neuroplasticity and that ultrastructural modulation of the neuronal circuits is of importance for the accomplishment of antipsychotics' particular effects. Roughly, if the treatment for schizophrenia is successful, that implies synaptic connectivity changes (modulation and facilitation of the synaptic plasticity).

Leveque JC. et al. (2000) approach in a similar ideologic context the fact that although antipsychotics produce effects on cerebral receptors, especially on the dopaminergic ones, the specific therapeutic effect mechanism seems far from being utterly elucidated. When interpreting resulting data of the experimental study, the quoted authors underline that haloperidol alters NMDA R activity by means of an intraneuronal mechanism. By facilitating the glutamatergic function, they produce an increase in neuronal sensitivity to the neurotoxic effects of glutamate. In patients with normal glutamatergic activity, haloperidol potentiate glutamate's normal neurotoxicity, while in patients with slightly lowered glutamate levels, the glutamate itself compensates the hypofunction in glutamatergic neurotransmission. This correlates tardive dyskinesia with cerebral glutamatergic hypofunction. Clozapine has no relevant modulating effects on NMDA R at therapeutic plasma levels.

Laruelle M. et al (2005) admits as working hypothesis that the fundamental mechanisms of schizophrenia are yet tentative. The dysfunctions in schizophrenia are associated to excessive DA function in subcortical areas, abnormality which could be secondary to a synaptic dysconnectivity in the prefrontal cortex, aspect which can be **psychochemically modeled by administration of NMDA antagonist**. A deficit in dopaminergic neurotransmission generates the dopaminic endophenotype associated to the disease, the dopaminic dysfunction being able, in itself, to emphasize the glutamatergic deficit. This could be the background on which the authors try to assemble, based on imagistic data, a relevant model for the pathogeny of schizophrenia which would correlate glutamate/dopamine and dopamine/glutamate. A deficit of glutamatergic transmission generates the dynamic endophenotype with the disease characteristics, the altering of dopaminergic exacerbating this glutamatergic deficit.

Recently, new approaches on antipsychotic treatment consequences appeared. Between 18 and 55 years of age in human, the ratio between myelinated white matter and grey matter changes, brain weight remaining constant. This extensive myelinisation process increases the brain capacity to process information, offering support for some

human capacity, such as language (Bartzokis G. et al, 2007). Human brain myelinisation process vulnerability contributes to the prevalence of some disorders of development, e.g. schizophrenia, autism, bipolar disorders, but also in addiction process (Bartzokis G, 2005; Bartzokis G. and Altshuler L., 2005). The cited authors consider that myelinisation process perturbing can contribute to schizophrenia syndrome, fact demonstrated by in vivo and post-mortem studies.

By imagistic resonance investigation (IR) method, very sensitive to cholesterol concentration in myelin (cholesterol reaches its highest concentration in myelin, compared with other tissues), it is analysed the differentiated effect of atypical antipsychotics compared with typical ones. In a clinical study Bartzokis G. et al (2007) used flufenazine decanoate (51 schizophrenic patients) and risperidone (20 schizophrenic patients) compared with a healthy control group. It resulted that frontal lobe size does not differ between the two treatment groups treated with flufenazine and risperidone, although the frontal lobe for those treated with flufenazine was reduced compared with the control group. Between the two treatment groups, differences appeared it concerns myelinated volume changes, specifying that schizophrenics have a smaller volume, compared with healthy volunteers group.

For the schizophrenic patients treated with risperidone, the myelinated volume was increased, at frontal lobe level, and decreased for flufenazine, compared to control group, although total frontal lobe volume didn't change. The mechanism for promyelinated effect of atypical antipsychotics is not yet defined, it may be correlated with lipid metabolic changes (weight gain) or a neuro-chemical mechanism consisting of dopaminergic neurotransmission increase at prefrontal cortex level, as support of the beneficial effect of atypical antipsychotics.

Lysergic acid diethylamide (LSD, Lisergamide), a highly active hallucinogen, produces a transitory psychosis in humans which comports profound altering of perception, behavior and mood, very much similar to schizophrenia.

The effects are considered consecutive to the interaction with serotonin receptors, subtypes 5HT2A, 5HT2C and 5HT1A, with agonist effect, but also with dopaminergic receptors for which LDS has high affinity.

LSD does not only produce rapid and reversible psychochemical effects, it also modifies the expression of certain genes in the mammal brain. An experimental study on rats conducted by Nichols CD. and Sanders-Bush show that LSD doubles C-fos expression at 90 minutes from administration. C-fos codes for the nuclear transcription factor which, in its own turn, controls multiple genes. This increase in C-fos determines neuronal activation. The authors describe the activation of other two genes which code for transcription factors. Another gene with LSD-increased expression is arc (activity regulated cytoskeletal-associated protein), an early gene involved in cytoskeletal rearrangement during synaptic plasticity.

The authors consider that the described processed not only refer to the acute mechanism of LSD action, but also reflect the beginning of a long neuroadaptive process.

Gene expression reflects the cellular requirements consecutive to the environmental change, in either physiologic of pathologic circumstances (Pollok JD., 2002).

In a recent synthesis (2006) Marder E and Goaillard JM, analyze the homeostatic mechanisms which account for the neuronal net stability throughout the individual's life. That derives into a similar behavior, as median result of processes of maximum complexity.

Man and animals with long life span have neurons which live and function for several decades. As opposed to the per-say neurons, the ionic channels, synaptic receptors and the components of signal transduction pathways are continually recycled in the membrane and replaced, with a half-life of minutes, hours or weeks. The neurons constantly reconstruct themselves, using their own molecular mechanisms to that end. These mechanisms allow for plastic modification of processes such as development and learning, but also confer a stability of neuronal function in the context of the perpetual change in the proteins which confer its electrophyisiologic characteristics.

In an excellent recent synthesis Tsankova N. et al (2007) analyses **the epigenetic mechanisms** which, through control of gene expression, without altering the genetic code, can generate stable changes of cerebral functions. The altering of gene expression is considered a molecular mechanism of response to chronic environmental changes such as frequent intake of abuse drugs, other drugs among which antipsychotics and antidepressants can be mentioned, chronic stress etc. The induced alterings can persist for weeks, but the behavioral aspects are stable and long lasting, even if their molecular

foundation is not yet defined.

The change in gene expression is consecutive to chromatin remodeling which is a dynamic process. Chromatin is a complex which consists of DNA, histones and other non-histone proteins. The fundamental unit of chromatin is composed of nucleosome (roughly 147 base pairs assembled round a histone octamer which contains two copies of each of the histones: H2A, H2B, H3 and H4). Chromatin can be found inactive outline, called heterochromatin (does not allow gene transcription) and under active state, euchromatin, which allows transcription of individual genes. The authors mention that real-life "live" chromatin can be found in multiple intermediate phases.

Chromatin remodeling is done through covalent reaction of the aminoacid residuum found on the histones' amine group. At this level acetylation, ubiquitination, methylation, phosphorylation and ADP ribosylation take place. Hyperacetylation bears the result of dispersed chromatin and increasing gene activity. Methylation can either lead to gene activation or repression, as can phosphorylation. The mentioned processes are controlled by enzymatic systems such as histone-acetyl-transferase, histone-deacetylase or methyl-transferase.

Another mechanism for gene repression is DNA methylation through transfer of a methyl group from S-adenosyl-methionine to the cytosine residuum of the CpG dinucleotide sequence through the action of DNA methyl transferase. Chromatin remodeling is involved in neurodevelopment but is also important is the regulation of mature neurons.

Chromatin remodeling is thus correlated with gene activation or repressing through synaptic activity.

Certain external stimuli produce rapid alterings in cerebral histones – cocaine and antipsychotics lead to H4 histone acetylation and striate H3 histone phosphoacetylation. The most obvious of histone alterings takes place in immediate-early genes such as C-Fos. C-Fos transcription is rapidly induced by various factors such as cocaine, antipsychotics and convulsions.

Which are the steps through which neuronal activity and synaptic transmission send signals to the nucleus for the regulation of enzymes and other such chromatin remodeling proteins? One of the important neural genes is BDNF (Brain-derived neurotrophic factor) which is regulated by chromatin remodeling.

The epigenetic mechanisms are probably used for maintaining both cellular memory (for example the safeguarding of differential characteristics) as for preserving and strengthening the synaptic connections which **uphold the long term behavioral changes** (Colvis CM. et al., 2005).

The cognitive and behavioral deterioration in schizophrenia are widely known and accepted (in a synthetic way these characteristics have a defining significance for the disease in question), as they are also mentioned in certain other psychological dysfunctions such as depression or bipolar disease (Lieberman JA., 1999). These phenomena are correlated, (proven through imagistic display or post-mortem), with neurodegenerative processes, particularly with increased neuronal mortality rate without compensation through neurogenesis (we shall revisit this aspect upon correlating it to the effect of antidepressants and antipsychotics).

According to Gratacos M. et al (2007) the phenomenon of synaptic plasticity altering and of BDNF is a common element in schizophrenia and also comports consecutive drug abuse or eating disorders. In a recent clinic study Gama CS. et al (2007) observed the effects of antipsychotic medication (clozapine, typical and atypical antipsychotics) on the plasma BDNF level. The selected patients were stabilized and had no prior admission in the past 5 years. The BDNF level in schizophrenic patients, under treatment, was considerably higher compared to the determined level in healthy volunteers. No differences were noticed in BDNF levels under clozapine, typical and atypical antipsychotics. The authors consider that the increased BDNF level might be a reaction to the neurodegenerative deterioration or it might be consecutive to the fact that during the chronic phase the metabolic aggression on the brain is reduced. The authors believe that this increase in BDNF correlates to the evolutive course of schizophrenia itself or can be a consequence of administration of antipsychotics.

In a review paper, Klan E. and Dever Th.E. (2004) analyze the molecular mechanisms of synaptic plasticity and long term memory (which need proteine synthesis), aspects correlated to gene expression modification. In this circumstance BDNF or glutamate R agonists induce the synthesis of new proteins, the local synthesis playing an essential role in synaptic plasticity and memory. The signaling pathways couple various membrane receptors with the onset of protein synthesis translation, with a subtle neuronal regulation of this process, as response to a particular synaptic impulse.

According to Manji HK. et al., (2003), the acute symptomatology of schizophrenia is at least partially modulated by the dopaminergic and glutamatergic signaling, while the chronic course of the disease is mediated by disturbance in neuronal development, maturation and functional plasticity (quoting Hirrsch and Weinberger, Schizophrenia, Blackwell Sci, Malden, MA, 2003 and Lewis DA., Lewitt P., 2002).

Takahashi M. et al (2000) demonstate that BDNF is considerably increased in the hippocampus (2-3 times) and in the anterior cingulate gyrus in schizophrenics compared to control. Other previous research showed that various altered molecular markers are results of the antipsychotic treatment. In the present study, an apparent dissociation isn't made between those treated with antipsychotics and those who withdrew themselves from the treatment. Is there any lasting effect post discontinuance?

In rats, the chronic haloperidol treatment does not increase but on the contrary, it decreases the BDNF level (authors note: in normal, healthy rats!). The authors believe that the high BDNF level in schizophrenia is a characteristic of the disease and not a consequence of the antipsychotic treatment. The BDNF receptor level, respectively Trk B level is low in the corticolimbic structures in schizophrenia and it inversely correlates to the BDNF level in the hippocampus.

The authors wonder if that particular decrease is the result of heightened BDNF release or if it's a disease correlated fault. Either way, BDNF signaling is perturbed.

The BDNF expression is influenced by various neurotransmitters out of which an intensely positive role belongs to glutamate. The compounds which are NMDA receptor antagonists decrease the BDNF expression in the hippocampus in rats or reduce the cerebral circulation in the respective areas in patients.

The authors notice that this increase in BDNF expression in schizophrenia cannot be explained by local neuronal excitability. BDNF/Trk B abnormalities in schizophrenic patients can make for a molecular foundation both for the structural and phenotypical dysfunctions in the respective disease.

In a metaanalysis on BDNF populational polymorphism in drug abuse, eating disorders and schizophrenia, Gratacòs M. et al (2007) discern that the BDNF allele Val 66 Met increases by 83% the risk for eating disorders but confers protection from substance abuse. The Met variant (allele) of BDNF which protects from drug abuse is also a risk factor for eating disorders and schizophrenia. In a synthesis by Angelucci F. et al (2005) the decrease of BDNF in schizophrenics is emphasized in cortical areas and in the hippocampus and decrease of Trk B and BDNF receptor in the respective patients' serum. BDNF gene polymorphism is associated to schizophrenia.

Trk B receptor knock-out mice present behavioral symptoms similar to those replicated for schizophrenia in mice (Zörner B. et al, 2003). According to Angelucci et al the abnormal expression of BDNF produces neurodevelopment dysfunction and/or cytoarchitecture plasticity altering in adults, generating schizophrenia or depression; the antipsychotics or antidepressants counteract the neurotransmission and plasticity dysfunctions in schizophrenia or depression through regularization of BDNF.

Addressing the problem of the onset antipsychotics effect is unavoidable in the context of the present data which mentions altering of a factor which is essential to the cerebral function. Antipsychotics generate such considerable effects. We shall tackle the early (days) or late (weeks, months) onset of the effects.

In a recent study Kapur S. et al (2005) brought supplementary proof of early onset for the antipsychotic effect, as opposed to the general opinion that the effect is late, slowly progressive. In the forementioned study the authors use injectable administration of haloperidol and olanzapine, compared to placebo in patients with agitation symptoms. They demonstrate antipsychotic effects which are distinct compared to those which address agitation or other behavioral signs. The authors critically present the respective data, stressing on the injectable administration compared to the oral one, on the span of the „wash-out" interval issue for the studied patients and on the fact that this study only refers to the two mentioned antipsychotics.

The authors remind that both haloperidol and olanzapine occupy over 80% of the D2 R in striate and extrastriatal areas within the first hours subsequent to administration. The time span differences for attaining the maximum plasma concentration by haloperidol and olanzapine after intramuscular or oral administration differs by 4-5 times (40-60 minutes compared to 4-6 hours for haloperidol, 0,5 hours compared to 3,5 hours for olazapine, respectively). The given differences cannot account

for the late onset of the antipsychotic effect, which is a paradoxal and relatively infrequent aspect for pharmacotherapy. In this case, the authors refer to the dissociation between the early D2 receptor occupancy and the late onset of the antipsychotic effect. For pharmacologists, this late effect suggests the involvement of a link which has the consequence of resetting a highly complex system by rearranging receptor population, changing the quantitave neuromediator/receptor ratios, synthesizing certain synaptic components, synaptic plasticity etc.

The discussion on dopaminergic receptors modulation process was reiterated at one time with interpretation of mechanisms for aripiprazole psychopharmacological effects. It was interpreted as modulation, in a first phase, and stabilization, subsequently, with known therapeutic consequences. In this context, we have suggested that D2 R modulation by a partial agonist may be followed by reseting, in the context of dopaminergic system interrelations with other neurotransmitters systems and only at this stage we can talk, eventually, about stabilization as a long duration process (Voicu VA, 2005).

The idea of optimal modulation of D2 receptors appears some years prior and it is considered as necessary and sufficient condition in order to obtain antipsychotic activity (Kapur S. and Seeman P., 2001).

What is intriguing is the fact that the issue of antipsychotic (and antidepressant) effect onset preoccupies the world of psychopharmacologists, thus struggling for balance between the action particularities of the respective compounds and the genesis of the antipsychotic effect in a system where the receptor population counter-regulations, the neurotransmission regulation and the response of the involved structures for preservation of the complex function of the neural net are notorious.

To this respect we evoke the issues correlated to plastic altering of the synapses preceded by changes in the expression of certain genes consecutive to long term blocking of the receptors in the concerned areas in the pathogenesis of schizophrenia (Hyman SE. and Nestler EJ., 1996).

Kapur S. et al (2001) mentions that dopamine depletion through alpha-methyl-p-tyrosine produces a major antipsychotic effect in 48 hours, suggesting that the interruption of the dopaminergic transmission on D2 R level is the immediate „mediator" of the antipsychotic response. In our opinion, this evokes the depletion effects of reserpine on cerebral and peripheral of monoamines (DA, NA and A), effects considered at that time "neuroleptic" (through monoaminergic depletion and receptors hypersensitization), with consequences which now, looking back, illustrate the current progresses in pharmacologic control of the dopaminergic dysfunction in schizophrenia.

In a recent article, Li M. et al (2007) reassess the issue of the apparent temporal dissociation between virtually immediate blocking (hours) of dopaminergic D2 R and the symptomatic amelioration of schizophrenia which only manifests after 2-3 weeks. Further research, such as **the ones we have presented**, evoke an onset within the first day or within the first week with exponential growth of symptomatic amelioration during the next 2-3 weeks. It must mention the fact that the therapeutic benefit is **more prominent as growth rate within the first few days**.

Kapur S. et al (2005) bring supplementary proof to favor their option on early onset of the antipsychotic effect on an experimental behavior model, respectively the conditioned avoidance response in a rat under antipsychotic treatment (haloperidol and olanzapine) compared to a rat under tranquilizing (anxiolytic) treatment with chlordiazepoxide. They notice that only after repeated antipsychotic treatment, (not subsequent to anxiolytic treatment), a progressive downward slope with early onset of avoidal response can be discerned. This type of phenomenon disappears after discontinuing the antipsychotics. The authors consider that the early diminishing phenomenon of conditioned avoidance produced by antipsychotics and not by anxiolytics cannot be attributed to the plain sedation through secondary motor effects. In our opinion, though, the sedative and/or anxiolytic effects of the two substance classes are accomplished, at least partially, by distinct pharmacodynamic mechanisms and are not comparable. One may ask what will be the consequence in case of comparison with an non-sedativ anxiolytic of buspirone type (5HT1A agonist) (Ichikawa J. et al, 2001).

Neuroplasticity manifests through the reorganization of synaptic connections as response to environmental changes. In this process, a considerable role is played by cortical inhibitor as the main component of the balance between inhibitory and excitatory processes (Daskalakis ZJ. et al, 2007). A function of major importance to the cortical inhibition is the mediation of cognitive operations, memory included. The morphologic foundation

for cortical inhibitory processes is represented by GABA interneurons, as Benes' FM. et al. (1991) research points out.

The inhibitory deficit of GABA interneurons produces an excessive inhibition through dopamine on the cortical GABAergic neurons with the consequence of increasing cortical excitability, respectively a non-modulated cortical activation with psychotic and neuromotor abnormalities. The critical endophenotype configured by inhibitory GABA deficit in schizophrenia accounts for the psychotic and cognitive dysfunction in schizophrenia (Daskalakis ZJ. et al., 2007). The pharmacologic control via facilitating GABA activity by atypical antipsychotics is proof of the validity of these interpretations (clozapine).

Neurobiological modulation - resetting and pharmacotherapeutic effects of antipsychotics

The consequences of long term administration of antipsychotics (and other additional drugs) are apparent on the expression of the genes which control the targets for the respective compounds. The outcome is the increase or altering of the expression of genes such as those which control the synaptic function, intracellular calcium concentration, K^+ channel expression, 5-HT2 receptor expression, that of the DA system, signal transduction, transcription regulation etc.

The plasticity processes in neuronal circuits along with neurogenesis in adults represent phenomena which reflect the quintessence of the complex biologic systems' assembly: stability and flexibility. The blend of stability and flexibility can be noticed in the whole genome. The newly shaped neurons which emerge in certain regions of the brain (the hippocampus and olfactive bulb) have adaptive functions which are priorly stipulated and different from those of the preexisting neurons and can eventually even replace dead neurons.

Cerebral plasticity deals with the brain's ability to change its structure and function in the maturation or learning processes, in environmental changes or in pathology. In other words, cerebral plasticity is an adaptive response to the challenges brought upon the organism by the environment of its own internal setting (Lledo PM et al., 2006).

In **Figure. 4** we present an outline of these interrelations.

These changes comport mechanisms which are involved in different levels of molecular structuring, and which occur in system alterings which concomitantly address neural elements, supportive glial structures and afferent blood vessels.

In brain pathology, including psychiatric dysfunctions (together with experimental models) we notice alterings in the morphology of neuron subpopulation, neurochemical modifications in the synaptic cleft, altering of the intracellular signaling and changes in gene expression (Tsankova N. et al, 2007).

Gene expression regulation is a molecular mechanism which might mediate the stable adjustings and the cerebral misadaptations.

Antipsychotics	Regulation							
	Striate				Cortex			
	D2	D4	D1	D5	D2	D4	D1	D5
TYPICAL								
Chlorpromazine	↑	↑	↔	↔	↑	↑	↓	↓
Haloperidol	↑	↑	↔	↔	↑	↑	↓	↓
Molindone	↑	↔	↔	↔	↑	↔	↓	↓
Pimozide	↑	↔	↔	↔	↑	↔	↓	↓
ATYPICAL								
Clozapine	↔	↑	↔	↔	↑	↑	↓	↓
Olanzapine	↔	↑	↔	↔	↑	↑	↓	↓
Remoxipirid	↑	↔	↔	↔	↑	↔	↓	↓
Risperidone	↑	↑	↔	↔	↑	↑	↓	↓
NON-ANTIPSYCHOTIC								
Tiaprid (D2 blocant)	↑	↑	↔	↔	↔	↑	↓	↓

Table V –D1/D2 regulation – A new equilibrium. The effect of chronic antipsychotic treatment of the level of mARN which codes varied dopaminergic R in the cortex and in the neostriate (modified after Lidow et al, TIPS, 1998, 19, April, 136-140)

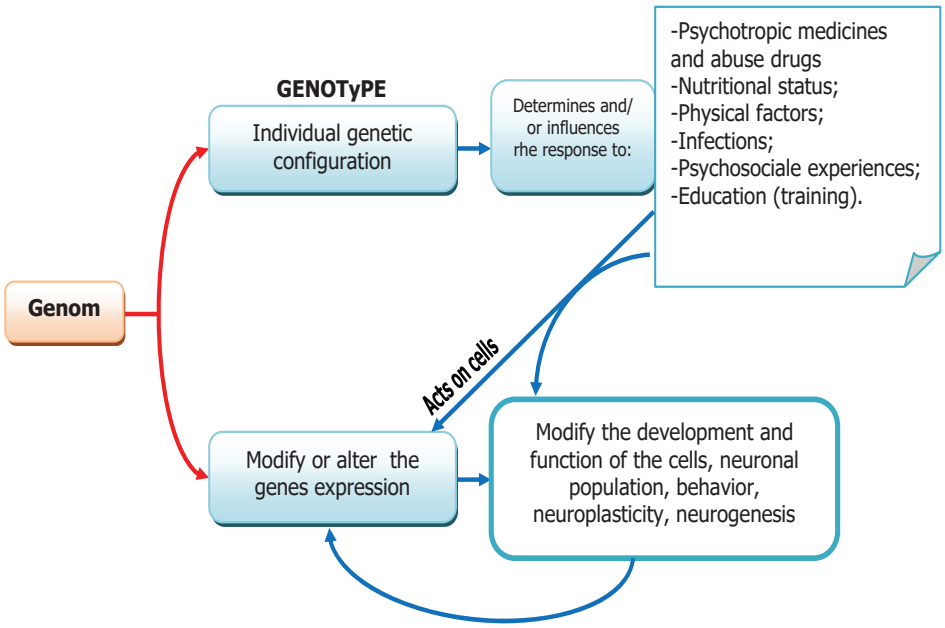

Figure. 4 – The dynamic interrelations between the genome and the environmental factors as a whole. The (epigenetic) consequences on gene expression

The psychiatric therapy with chronic administration virtually needs to manage the patient up to a full recovery. This context comports the understanding of the molecular mechanisms behind reversing the alterations in schizophrenia, respectively through pharmacodynamic mechanism (Tsankova N. et al, 2007) on one hand and also the complex consequences of this initial phase and the achievement of therapeutic antipsychotic effect.

The nervous system rapidly adapts to environmental changes without genetic mutations through the coordination and correlation of external and internal data. Thus, a functional response is elaborated through complex effectors systems which manage to maintain homeostasis.

The harmonic merging of two tendencies: stability and flexibility can be obtained by the organism through a continual change of gene expression regulation (epigenetic mechanisms) only through chromatin reshaping with no modification in the DNA sequence (Colvis CM. et al, 2005). This neurobiologic concept of chromatin remodeling explains how, through gene expression altering (which can become transmissible) at neuronal and glial level, long lasting behavioral changes occur. These aspects have a solid scientific foundation, relevant both clinically and experimentally.

The data outlined in this synthesis permits acknowledgement that multireceptor effects of antipsychotics are concluded by regulations and counter-regulations of the processes which correspond to different neurotransmissions (receptor activation or inactivation, quantitative changes in the synthesis and release of neuromediators, altering homeostatic function interrelation between various interconnected neuromediation systems etc.) (**Figure 4**). These low-latency homeostatic phenomena serve as signals for other, slower, more complex phenomena involving altering the expression of certain genes which code for the synthesis of the involved cerebral receptors (up and downregulation) (Lidow et al., 1998) synthesis, transportation, depositing and release of neuromediators, synaptic plasticity and/or neuroplasticity. In the given context we could mention a pharmacotherapeutic phase, if this brings relevant data, with the clinical frame stabilizing.

The process of gene expression modulation consecutive to the impact of environmental conditions (which include chronically administered drugs, abuse drugs, smoking etc.) (Voicu VA., 2005) can be considered the organism's engine for adapting and evolving.

All these complex processes generated by antipsychotics have unavoidable consequences on the symptomatology of schizophrenia, the receptor level interaction being considered an initiation of a complex process which shall generate a new equilibrium produced through alterings in the expression

of the target genes. If the genome is characterized by stability, the epigenetic altering can explain the variability of inter- and especially intraindividual response to antipsychotics.

As a consequence of the complex actions initiated by antipsychotics in the pharmacodynamic phase, an intricate process of resetting for the systems which are gravely altered in schizophrenia has been thought-up. The resetting of the system is beneficial and possibly relevant for the end-point of antipsychotic therapy.

References

1. Andersson C, Hamer RM, Lawler CP, Mailman RB, Lieberman JA., Striatal volume changes in the rat following long-term administration of typical and atypical antipsychotic drugs, *Neuropsychopharmacology.* **2002 Aug;27(2):143-51.**

2. Angelucci F, Brenè S, Mathé AA., BDNF in schizophrenia, depression and corresponding animal models, *Mol Psychiatry.* **2005 Apr;10(4):345-52.**

3. Aravagiri M., Teper Y., Marder SR., Pharmacokinetics and tissue distribution of olanzapine in rats **,** *Biopharm Drug Disp***, 1999, 20(8), 369-377.**

4. Arnt J, Skarsfeldt T., Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence, *Neuropsychopharmacology.* **1998 Feb;18(2):63-101.**

5. Arranz MJ, de Leon J., Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research, *Mol Psychiatry.* **2007 Aug;12(8):707-47.**

6. Bartzokis G, Lu PH, Mintz J., Human brain myelination and amyloid beta deposition in Alzheimer's disease, *Alzheimers Dement.* **2007 Apr;3(2):122-125.**

7. Bartzokis G., brain myelination in prevalent neuropsychiatric developmental disorders: primary and comorbid addiction, *Adolesc Psychiatry.* **2005;29:55-96.**

8. Bartzokis G., Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation, *Neuropsychopharmacology.* **2002 Oct;27(4):672-83.**

9. Benes FM, McSparren J, Bird ED, SanGiovanni JP, Vincent SL., Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients, *Arch Gen Psychiatry.* **1991 Nov;48(11):996-1001.**

10. Bozzi Y, Vallone D, Borrelli E., Neuroprotective role of dopamine against hippocampal cell death, *J Neurosci.* **2000 Nov 15;20(22):8643-9.**

11. Buckley PF., Receptor-binding profiles of antipsychotics: clinical strategies when switching between agents, *J Clin Psychiatry.* **2007;68 Suppl 6:5-9.**

12. Carlsson A., Antipsychotic drugs, neurotransmitters, and schizophrenia, *Am J Psychiatry.* **1978 Feb;135(2):165-73.**

13. Carlsson A., Waters N., Carlsson ML., Neurotransmitter interaction in schizophrenia - therapeutic implications, *Biol. Psychiatry,* **1999, 46, 10, 1383-1395.**

14. Centonze D, Grande C, Saulle E, Martin AB, Gubellini P, Pavón N, Pisani A, Bernardi G, Moratalla R, Calabresi P., Distinct roles of D1 and D5 dopamine receptors in motor activity and striate synaptic plasticity, *J Neurosci.* **2003 Sep 17;23(24):8506-12.**

15. Chambers RA, Potenza MN, Hoffman RE, Miranker W., Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks, *Neuropsychopharmacology.* **2004 Apr;29(4):747-58.**

16. Chen ML, Chen CH, Microarray Analysis of Differentially Expressed Genes in Rat Frontal Cortex Under Chronic Risperidone Treatment, *Neuropsychopharmacology,* **(2005), 30, 268–277.**

17. Chen ML, Chen CH., Chronic antipsychotics treatment regulates MAOA, MAOB and COMT gene expression in rat frontal cortex, *J Psychiatr Res.* **2007 Jan-Feb;41(1-2-):57-62.**

18. Citri A, Malenka RC., Synaptic plasticity: multiple forms, functions, and mechanisms, *Neuropsychopharmacology.* **2008 Jan;33(1):18-41.**

19. Cochran SM, Kennedy M, McKerchar CE, Steward LJ, Pratt JA, Morris BJ., Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: differential modulation by antipsychotic drugs, *Neuropsychopharmacology.* **2003 Feb;28(2):265-75.**

20. Colvis CM, Pollock JD, Goodman RH, Impey S, Dunn J, Mandel G, Champagne FA, Mayford M, Korzus E, Kumar A, Renthal W, Theobald DE, Nestler EJ., Epigenetic mechanisms and gene networks in the nervous system, *J Neurosci.* **2005 Nov 9;25(45):10379-89.**

21. Cowen SD., Serotonine and neuronal grouth factors - convergence of signalling pathway, *J.Neurochem.,* **2007, 101, 1161-1171.**

22. Daskalakis ZJ, Fitzgerald PB, Christensen BK., The role of cortical inhibition in the pathophysiology and treatment of schizophrenia, *Brain Res Rev.* **2007 Dec;56(2):427-42.**

23. Davis JM, Chen N., Old versus new: weighing the evidence between the first- and second-generation antipsychotics, *Eur Psychiatry.* **2005 Jan;20(1):7-14.**

24. Dean CE., Antipsychotic-associated neuronal changes in the brain: toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia?**,** *Prog Neuropsychopharmacol Biol Psychiatry.* **2006 Mar;30(2):174-89.**

25. Duman RS., Nakagawa S., Malberg J., Regulation of adult neurogenesis by antidepressant treatment, *Neuropsychopharmacol.***, 2001, 25(6), 836-844.**

26. Duman RS., Synaptic plasticity and mood disorders, *Mol Psychiatry.* **2002;7 Suppl 1:S29-34.**

27. Eastwood SL, Harrison PJ., Cellular basis of reduced cortical reelin expression in schizophrenia, *Am J Psychiatry.* **2006 Mar;163(3):540-2.**

28. Eastwood SL, Heffernan J, Harrison PJ., Chronic haloperidol treatment differentially affects the expression of synaptic and neuronal plasticity-associated genes, *Mol Psychiatry.* **1997 Jul;2(4):322-9.**

29. Fatemi SH, Reutiman TJ, Folsom TD, Bell C, Nos L, Fried P, Pearce DA, Singh S, Siderovski DP, Willard FS, Fukuda M., Chronic olanzapine treatment causes differential expression of genes in frontal cortex of rats as revealed by DNA microarray technique, *Neuropsychopharmacology.* **2006 Nov;31(11):2567.**

30. Fatemi SH., Reclin glycoprotein: structure, biology and roles in health and diseases, *Molec.Psychiatry,* **2005, 10, 251-257.**

31. Fatemi SH., Reelin glycoprotein in autism and schizophrenia, *Int Rev Neurobiol.* **2005;71:179-87.**

32. Fehér LZ, Kálmán J, Puskás LG, Gyülvészi G, Kitajka K, Penke B, Palotás M, Samarova EI, Molnár J, Zvara A, Matin K, Bódi N, Hugyecz M, Pákáski M, Bjelik A, Juhász A, Bogáts G, Janka Z, Palotás A., Impact of haloperidol and risperidone on gene expression profile in the rat cortex, *Neurochem Int.* **2005 Sep;47(4):271-80.**

33. Frazer A, Benmansour S., Delayed pharmacological effects of antidepressants, *Mol Psychiatry.* **2002;7 Suppl 1:S23-8.**

34. Friston KJ, Frith CD, Fletcher P, Liddle PF, Frackowiak RS., Functional topography: multidimensional scaling and functional connectivity in the brain, *Cereb Cortex.* **1996 Mar-Apr;6(2):156-64.**

35. Friston KJ., Disconnection and cognitive dissymmetry n schizophrenia, *Am J Psychiatry.* **2005 Mar;162(3):429-32.**

36. Frost DO, Tamminga CA, Medoff DR, Caviness V, Innocenti G, Carpenter WT., Neuroplasticity and schizophrenia, *Biol Psychiatry.* **2004 Oct 15;56(8):540-3.**

37. Gama CS, Andreazza AC, Kunz M, Berk M, Belmonte-de-Abreu PS, Kapczinski F., Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder, *Neurosci Lett.* **2007 Jun 8;420(1):45-48.**

38. Gerber DJ, Tonegawa S., Psychotomimetic effects of drugs--a common pathway to schizophrenia?**,** *N Engl J Med.* **2004 Mar 4;350(10):1047-8.**

39. Gogos JA, Gerber DJ., Schizophrenia susceptibility genes: emergence of positional candidates and future directions, *Trends Pharmacol Sci.* **2006 Apr;27(4):226-33.**

40. Gogos JA., Schizophrenia susceptibility genes: in search of a molecular logic and novel drug targets for a devastating disorder, *Int Rev Neurobiol.* **2007;78:397-422.**

41. Gordon Frankle W, Lerma J, Larnelle M, The synaptic hypothesis of schizophrenia, *Neuron,* **2003, 39, 206-216.**

42. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X., Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia, *Biol Psychiatry.* **2007 Apr 1;61(7):911-22.**

43. Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC., Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia, *Am J Psychiatry.* **1998 Dec;155(12):1711-7.**

44. Guterman Y., A neural plasticity perspective on the schizophrenic condition, Conscious Cogn. **2007 Jun;16(2):400-20.**

45. Harrison P., Neurobiology of schizophrenia, *Psychiatry,* **2005, 4(10): 18-21.**

46. Harrison PJ., The neuropathological effects of antipsychotic drugs, *Schizophr Res.* **1999 Nov 30;40(2):87-99.**

47. Harrison PJ., The neuropathology of schizophrenia. A critical review of the data and their interpretation, *Brain.* **1999 Apr;122 (Pt 4):593-624.**

48. Harrison PJ., Weinberger DR., Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence, *Mol Psychiatry.* **2005 Jan;10(1):40-68.**

49. Harrison PJ., Weinberger DR., Schizophrenia genes, gene expression and neuropathology: as the matter of their convergence., *Molec.Psychiatry,* **2005, 10, 40-68.**

50. Heikkinen AE, Möykkynen TP, Korpi ER., Long-lasting modulation of glutamatergic transmission in VTA dopamine neurons after a single dose of benzodiazepine agonists, *Neuropsychopharmacology.* **2009 Jan;34(2):290-8.**

51. Heimer L., A new anatomical framework for neuropsychiatric disorders and drug abuse, *Am.J.Psychiatry,* **2003, 160, 1726-1739.**

52. Hill SJ., G-protein-coupled receptors: past, present and future, *Br J Pharmacol.* **2006 Jan;147 Suppl 1:S27-37.**

53. Hong JS, Huiwu L, Becker KG, Dawson VL, Dawson T., Identification and analysis of plasticity induced late-response genes, *PNAS,* **2004, 101, 7, 2145-2150.**

54. Huang XF, Han M, Huang X, Zavitsanou K, Deng C., Olanzapine differentially affects 5-HT2Aand2C receptor mRNA expression in the rat brain, *Behav Brain Res.* **2006 Aug 10;171(2):355-62.**

55. Huang XF, Tan YY, Huang X, Wang Q., Effect of chronic treatment with clozapine and haloperidol on 5-HT(2A and 2C) receptor mRNA expression in the rat brain, *Neurosci Res.* **2007 Nov;59(3):314-21.**

56. Hyman SE, Nestler EJ., Initiation and adaptation: a paradigm for understanding psychotropic drug action, *Am J Psychiatry.* **1996 Feb;153(2):151-62.**

57. Iasevoli F, Polese D, Ambesi-Impiombato A, Muscettola G, de Bartolomeis A., *Ketamine-related expression of glutamatergic postsynaptic density genes: possible implications in psychosis, Neurosci Lett.* **2007 Apr 6;416(1):1-5.**

58. Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY., 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release, *J Neurochem.* **2001 Mar;76(5):1521-31.**

59. Kalivas PW, O'Brien C., Drug addiction as a pathology of staged neuroplasticity, *Neuropsychopharmacology.* **2008 Jan;33(1):166-80.**

60. Kapur S, Agid O, Mizrahi R, Li M., How antipsychotic work – from receptor to reality, *J.Am.Soc.Exper.Neurotherap.,* **2006, 3, 10-21.**

61. Kapur S, Arenovich T, Agid O, Zipursky R, Lindborg S, Jones B., Evidence for onset of antipsychotic effects within the first 24 hours of treatment, *Am J Psychiatry.* **2005 May;162(5):939-46.**

62. Kapur S, Mamo D., Half a century of antipsychotics and still a central role for dopamine D2 receptors, *Prog Neuropsychopharmacol Biol Psychiatry.* **2003 Oct;27(7):1081-90.**

63. Kapur S, Remington G., Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient, *Biol Psychiatry.* **2001 Dec 1;50(11):873-83.**

64. Kapur S, Seeman P., Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis, *Am J Psychiatry.* **2001 Mar;158(3):360-9.**

65. Kenakin T., Inverse, protean, and ligand-selective agonism: matters of receptor conformation, *FASEB J.* **2001 Mar;15(3):598-611.**

66. Klan E., Dever Th..E., Biochemical mechanisms for translational regulation in synaptic plasticity, *Nature Rev. Neurosci.,* **2004, Dec, 931-942.**

67. Konradi C, Heckers S., Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment, *Pharmacol Ther.* **2003 Feb;97(2):153-79.**

68. Konradi C., Heckers S., Antipsychotic drugs and neuroplasticity: insights into the treatment and neurobiology of schizophrenia, *Biol.Psychiatry,* **2001, 50, 729-742.**

69. Kontkanen O., Toronen P., Lesko M., Wong G., Castren E., Antipsychotic drug treatment reduces differential gene expression in the rat cortex, *J.Neurochemistry,* **2002, 83, 1043-1053.**

70. Laruelle M, Frankle WG, Narendran R, Kegeles LS, Abi-Dargham A., Mechanism of action of antipsychotic drugs: from dopamine D(2) receptor antagonism to glutamate NMDA facilitation, *Clin Ther.* **2005;27 Suppl A:S16-24.**

71. Leveque JC, Macías W, Rajadhyaksha A, Carlson RR, Barczak A, Kang S, Li XM, Coyle JT, Huganir RL, Heckers S, Konradi C., Intracellular modulation of NMDA receptor function by antipsychotic drugs, *J Neurosci.* **2000 Jun 1;20(11):4011-20.**

72. Lewis DA, González-Burgos G., Neuroplasticity of neocortical circuits in schizophrenia, *Neuropsychopharmacology.* **2008 Jan;33(1):141-65.**

73. Lewis DA, Lieberman JA., Catching up on schizophrenia: natural history and neurobiology, *Neuron.* **2000 Nov;28(2):325-34.**

74. Li M, Fletcher PJ, Kapur S., Time course of the antipsychotic effect and the underlying behavioral mechanisms, *Neuropsychopharmacology*. **2007 Feb;32(2):263-72.**

75. Lidow MS, Elsworth JD, Goldman-Rakic PS., Down-regulation of the D1 and D5 dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs, *J Pharmacol Exp Ther.* **1997 Apr;281(1):597-603.**

76. Lidow MS, Williams GV, Goldman-Rakic PS., The cerebral cortex: a case for a common site of action of antipsychotics, *Trends Pharmacol Sci.* **1998 Apr;19(4):136-40.**

77. Lieberman JA, Jarskog LF, Malaspina D., Preventing clinical deterioration in the course of schizophrenia: the potential for neuroprotection, *J.Clin.Psychiatry,* **2006, 67(6), 983-990.**

78. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M; HGDH Study Group, Antipsychotic drug effects on brain morphology in first-episode psychosis, *Arch Gen Psychiatry.* **2005 Apr;62(4):361-70.**

79. Lledo PM, Alonso M, Grubb MS., Adult neurogenesis and functional plasticity in neuronal circuits, *Nat Rev Neurosci.* **2006 Mar;7(3):179-93.**

80. Malberg JE, Eisch AJ, Nestler EJ, Duman RS., Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus, *J Neurosci.* **2000 Dec 15;20(24):9104-10.**

81. Manji HK, Gottesman II, Gould TD., Signal transduction and genes-to-behaviors pathways in psychiatric diseases, *Sci STKE.* **2003 Nov 4;2003(207):pe49.**

82. Marder E, Goaillard JM., Variability, compensation and homeostasis in neuron and network function, *Nat Rev Neurosci.* **2006 Jul;7(7):563-74.**

83. McClung CA, Nestler EJ., Neuroplasticity mediated by altered gene expression, *Neuropsychopharmacology.* **2008 Jan;33(1):3-17.**

84. McQuade RD, Burris KD, Jordan S, Tattori K, Kurahashi N, Kikuchi T., Aripiprazole: a dopamine - serotonine system stabilizer (abstract), *Int.J.Neuropsychopharmacol.,* **2002, 5 (suppl.1).**

85. Meltzer HY, Matsubara S, Lee JC., Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values, *J Pharmacol Exp Ther.* **1989 Oct;251(1):238-46.**

86. Meshul CK, Bunker GL, Mason JN, Allen C, Janowsky A., Effects of subchronic clozapine and haloperidol on striatal glutamatergic synapses, *J Neurochem.* **1996 Nov;67(5):1965-73.**

87. Millan MJ., Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors, *J Pharmacol Exp Ther.* **2000 Dec;295(3):853-61.**

88. Mirnics K, Middleton FA, Lewis DA, Levitt P., *Analysis of complex brain disorders with gene expression microarrays: schizophrenia as a disease of the synapse, Trends Neurosci.* **2001 Aug;24(8):479-86.**

89. Muglia P, Vicente AM, Verga M, King N, Macciardi F, Kennedy JL., Association between the BDNF gene and schizophrenia, *Mol Psychiatry.* **2003 Feb;8(2):146-7.**

90. Myamoto S., Duncan GE., Marx IE., Liebermann JA., Treatment for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs, *Molec. Psychiatry,* **2005, 10, 79-104.**

91. Natesan S, Reckless GE, Nobrega JN, Fletcher PJ, Kapur S., Dissociation between in vivo occupancy and functional antagonism of dopamine D2 receptors: comparing aripiprazole to other antipsychotics in animal models, *Neuropsychopharmacology.* **2006 Sep;31(9):1854-63.**

92. Nichols CD, Sanders-Bush E., A single dose of lysergic acid diethylamide influences gene expression patterns within the mammalian brain, *Neuropsychopharmacology.* **2002 May;26(5):634-42.**

93. Owen MJ, Williams NM, O'Donovan MC., The molecular genetics of schizophrenia: new findings promise new insights, *Mol Psychiatry.* **2004 Jan;9(1):14-27.**

94. Paizanis E, Hamon M, Lanfumey L., Hippocampal neurogenesis, depressive disorders, and antidepressant therapy, *Neural plasticity,* **2007, ID 73754.**

95. Petronis A, Paterson AD, Kennedy JL., Schizophrenia: an epigenetic puzzle?, *Schizophr Bull.* **1999;25(4):639-55.**

96. Pollock JD., Gene expression profiling: methodological challenges, results, and prospects for addiction research, *Chem Phys Lipids.* **2002 Dec 31;121(1-2):241-56.**

97. Reynolds GP., Receptor mechanisms in the treatment of schizophrenia, *J Psychopharmacol.* **2004 Sep;18(3):340-5.**

98. Robert D., Strange Ph., Mechanisms of inverse agonist action at D2 dopamine receptors, *Brit.J.Pharmacol.*, **2005, 145, 34-42.**

99. Ross CA, Margolis RL, Reading SA, Pletnikov M, Coyle JT., Neurobiology of schizophrenia, *Neuron.* **2006 Oct 5;52(1):139-53.**

100.Rowan MJ, Anwyl R, Xu L., Stress and long-term synaptic depression, *Mol Psychiatry*. **1998 Nov;3(6):472-4.**

101.Scheepers FE, Gispen CC, Hulshoff HE, Kahn RS.,

Effect of clozapine on caudate nucleus volume in relation to symptoms of schizophrenia, *AM.J.Psychiatry,* **2001, 158, 644-646.**

102.Seeman P, Tallerico T., Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine, *Am J Psychiatry.* **1999 Jun;156(6):876-84.**

103.Shao Z, Dyck LE, Wang H, Li XM., Antipsychotic drugs cause glial cell line-derived neurotrophic factor secretion from C6 glioma cells, *J Psychiatry Neurosci.* **2006 Jan;31(1):32-7.**

104.Stephan KE, Baldeweg T, Eriston KJ, Synaptic plasticity and disconnection in schizophrenia, *Biol.Psychiatry,* **2006, 59: 929-939.**

105.Sthal S., Dopamine system stabilizers, aripiprazole, the next generation of antipsychotics, part 1, *J.Clin.Psychiatry,* **2001, 62(11), 841-842.**

106.Suzuki T, Miura M, Nishimura K, Aosaki T., Dopamine-dependent synaptic plasticity in the striatal cholinergic interneurons, *J Neurosci***. 2001 Sep 1;21(17):6492-501.**

107.Takahashi M, Shirakawa O, Toyooka K, Kitamura N, Hashimoto T, Maeda K, Koizumi S, Wakabayashi K, Takahashi H, Someya T, Nawa H., Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients, *Mol Psychiatry.* **2000 May;5(3):293-300.**

108.Tamminga CA, Holcomb HH., Phenotype of schizophrenia: a review and formulation, *Mol Psychiatry.* **2005 Jan;10(1):27-39.**

109.Tandon R, Greden JF, Haskett RF., Cholinergic hyperactivity and negative symptoms: behavioral effects of physostigmine in normal controls, *Schizophr Res.* **1993 Mar;9(1):19-23.**

110.Tandon R, Greden JF., Cholinergic hyperactivity and negative schizophrenic symptoms. A model of cholinergic/dopaminergic interactions in schizophrenia, *Arch Gen Psychiatry.* **1989 Aug;46(8):745-53.**

111.Tandon R, Taylor SF, DeQuardo JR, Eiser A , Jibson MD, Goldman M., The Cholinergic System in Schizophrenia Reconsidered: Anticholinergic Modulation of Sleep and Symptom Profiles, *Neuropsychopharmacol.,* **1999, 21, S189-S202.**

112.Tauscher J, Jones C, Remington G, Zipursky RB, Kapur S., Significant dissociation of brain and plasma kinetics with antipsychotics, *Mol Psychiatry.* **2002;7(3):317-21.**

113.Tononi G, Cirelli C., Modulation of brain gene expression during sleep and wakefulness: a review of recent findings, *Neuropsychopharmacology.* **2001 Nov;25(5 Suppl):S28-35.**

114.Toro CT, Deakin JF., Adult neurogenesis and schizophrenia: a window on abnormal early brain development?, *Schizophr Res.* **2007 Feb;90(1-3):1-14.**

115.Tsankova N, Renthal W, Kumar A, Nestler EJ., Epigenetic regulation in psychiatric disorders, *Nat Rev Neurosci.* **2007 May;8(5):355-67.**

116.Verhoeff NPLG, Hussey D, Lee M, Taucher J., Papatheodoru G, Wilson AA, Houle S, Kapur S., Dopamine depletion results in increased neostriatal D2, but not D1, receptor binding in human, *Molec.Psychiatry,* **2002, 7, 322-328.**

117.Voicu VA., Aripiprazole is atypical antipsychotic with a new mechanisms?, *Therapeutics, Clinical Pharmacology and Toxicology,* **2005, 9 (1), 7-16.**

118.Voicu VA., Clinical psychopharmacology and toxicology of abuse drugs, *Editura Academia Romana***, Bucuresti, 2005.**

119.Voicu VA., Rădulescu F., Gheorghe M., Pharmacodynamic and therapeutic effects of antipsychotics. Modulation and neurobiologic reseting (I), *Therapeutics, Clinical Pharmacology and Toxicology,* **2008, 12 (1), 11-25.**

120.Voicu VA., Rădulescu F., Gheorghe M., Pharmacodynamic and therapeutic effects of antipsychotics. Modulation and neurobiologic reseting (II), *Therapeutics, Clinical Pharmacology and Toxicology,* **2008, 12 (2), 179-191.**

121.Voicu VA., Radulescu F., Miron D., Mircioiu C, CYP 2D6 polymorphism and interindividual variability of drug response. A risperidone study case, *Rev.Med.Farm.Targu-Mures,* **2007, 53, 265-270.**

122.Volkow ND, Fowler JS, Wang GJ, Swanson J M, Telang F., Dopamine in drug abuse and addiction: results of imaging studies and treatment implications**,** *Arch Neurol.* **2007 Nov;64(11):1575-9.**

123.Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE., Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia, *Mol Psychiatry.* **2003 Jun;8(6):592-610.**

124.Zörner B, Wolfer DP, Brandis D, Kretz O, Zacher C, Madani R, Grunwald I, Lipp HP, Klein R, Henn FA, Gass P, Forebrain-specific trkB-receptor knockout mice: behaviorally more hyperactive than "depressive", *Biol Psychiatry.* **2003 Nov 15;54(10):972-82.**