A PHARMACOGENETIC AND DYNAMICAL MODEL OF THE RESISTANCE TO ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA

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It is accepted at present the neo-bleulerian theory, adapted to the organodynamic concept of Henri Ey (1). It explains the negative symptoms, consisting the primary deficit in schizophrenia with the dissolution of the higher neurobiological functions, demonstrated with hypoactivity of the prefrontal cortex.

This leads to hyperdopaminergic disinhibition (derepression) of older in evolution structures of the mesencephalo-limbic tractus, as well as the temporal polar cortex, acting in the determination of the positive symptoms in schizophrenia (such as delusions and hallucinations).

According to the D. Toncheva’s results(3), there is a reduced expression of dopamine-β-hydroxylase (DβH) gene, and increased expression of the dopamine-transporter (DAT) gene, both correlating with the positive symptoms (verbal hallucinations, for instance) in the significant number of clinically diagnosed patients.

From a pharmacogenetical view, these results are a premise for a pharmacodynamic hypothesis for the resistance of the positive symptoms in schizophrenia to neuroleptic (dopamine receptor antagonists) treatment. The decreased expression of DβH results in reduced enzymatic degradation of dopamine (DA) in the synaptic cleft. The persisting increased [DA] concentration stimulates the postsynaptic D2 receptors, then they respond adaptively, by down-regulation. The feed-back mechanism must decrease the DA synthesis, by inhibiting directly the tyrosine-hydroxylase (the pace-making, speed-limiting, reaction of the process), and by increasing the destruction of DA by DβH. Even if the first mechanism is intact, the second is insufficient. The available DA, meanwhile is transported to the synaptic terminal by DAT at a rate, that obstructs the effectiveness of the monoaminooxydase (MAO) catabolism in the vesicles. So the excess of DA is directed to exocytosis and neurotransmission without being destroyed. If there is a defect in the TH or in its cofactors, so to that supraphysiological (DA) there are joining the de novo produced DA molecules, in the synaptic space, so that the postsynaptic neuron reacts with tonic
excessive postsynaptic potentials and remains in a permanent state of excitation, that is irregular, due to the disturbed feedback with the presynaptic neuron. The reduced DβH, as well as the non-specific catechol-o-methyl–transferase (C-O-MT) can not eliminate the abnormal amount of DA because of the hyperactivity of the autoregulatory transporter (DAT). During the rapid recycling of DA the intracellular MAO, can not remove the excessive DA, also. The absolute number of the postsynaptic D2 receptors is decreasing (down-regulation), due to the continuous stimulation, signalling to the regulatory mechanisms to catabolise the excessive DA. So, because of their insufficiency and the rapid reuptake, realised by DAT, DA proceeds turning over in the “hurricane” or a vicious circle.

This phenomenon may explain some cases of resistance to antipsychotic treatment.

Neuroleptics (DA receptor antagonist), must block 65-85% of the expressed receptor proteins in order to induce remission (verified with positron-emission tomography therapeutic diapason (2)). Therefore the absolute DA concentration must decrease to physiological values, during their occupation. This does not occur, because of the described phenomenon, and most probably the excessive amount of the protoligand (the native DA), competes with the neuroleptic molecules for the D2 binding sites, and because of the higher affinity, removes them. At the background of 80% expression, there appears a compensatory up – regulation of the receptors, and regardless to the therapeutic saturation, DA proceeds binding to the unoccupied sites, and thus realises its pathobiochemical effects.

REFERENCES

On the 105th anniversary of the birth of French psychiatrist Henri Ey (10.08.1900-8.11.1977)