

PP9.2. NOVI MEHANIZMI DELOVANJA U RAZVOJU ANTIPSIHOTIKA: DOKAZI SA KLINIČKOG STANOVIŠTA

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Od otkrića antipsihotika pre više od 60 godina njihov mehanizam dejstva je povezan sa blokadom dopaminskih D2 receptora. Nova saznanja iz neuronauka su uslovlila pojavu antipsihotika sa drugačijim mehanizmom dejstva, ali još uvek vezanih za dopaminske D2 receptore. U tu grupu spadaju takozvani antipsihotici II generacije koji, pored značajnog afiniteta za dopaminske D2 receptore, imaju i značajan afinitet za serotoninske 5HT₂ receptore. Novi napredak je ostvaren razvojem parcijalnih D2 dopaminskih agonista. Ovi lekovi bi praktično činili III generaciju antipsihotika. Na ovaj način priča o antipsihoticima koji deluju prevashodno putem dejstva na dopaminske receptore je kompletirana. Ipak, značajan procenat pacijenata koji nezadovoljavajuće reaguju na ove antipsihotike, zatim značajni neželjeni efekti i, konačno, praktično odsustvo dejstva na negativne i pre svega kognitivne simptome shizofrenije uslovljava razvoj novih antipsihotika. Uz sve to, svi do sada poznati mehanizmi dejstva na dopaminske receptore su praktično postsinaptičke lokalizacije, dok naučna saznanja ukazuju da je dominantna disfunkcija lokalizovana presinaptički, na telu dopaminskog neurona. Sve ovo zahteva razvoj novih antipsihotika sa drugačijim mehanizmom dejstva.

Ovo predavanje daje kritički pregled novih farmakoloških pristupa i dostupnih kliničkih dokaza. Posebna pažnja posvećena je muskarinskim agonistima, pre svega kombinaciji xanomelin–trospijum. Njena efikasnost u kratkotrajnim studijama kod akutne šizofrenije je potvrđena, uz drugačiji profil neželjenih efekata, koji su pretežno gastrointestinalni i holinergički. Razmatraju se i agonisti TAAR1 receptora, modulatori glutamatergičke neurotransmisije, uključujući inhibitore transportera glicina, kao i lekovi usmereni na serotoninske receptore.

PP9.2. NEW MECHANISMS OF ACTION IN THE DEVELOPMENT OF ANTIPSYCHOTICS: EVIDENCE FROM A CLINICAL PERSPECTIVE

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For 60 years since the discovery of antipsychotics, their action has been linked to blockade of dopamine D2 receptors. New neuroscientific insights have led to antipsychotics with different mechanisms of action, yet still related to dopamine D2 receptors. This group includes the second-generation antipsychotics, which, in addition to affinity for dopamine D2 receptors, also have affinity for serotonin 5-HT₂ receptors. Further progress came with partial dopamine D2 agonists. These drugs constitute the third generation of antipsychotics. In this way, the story of antipsychotics that act primarily through effects on dopamine receptors has been completed.

Nevertheless, many patients show an unsatisfactory response to these antipsychotics, together with substantial adverse effects and, ultimately, a virtual lack of efficacy against negative and, above all, cognitive symptoms of schizophrenia, which necessitates the development of new antipsychotics. In addition, all mechanisms of action on dopamine receptors are practically of postsynaptic localization, whereas scientific evidence indicates that the dominant dysfunction is localized presynaptically, on the cell body of the dopamine neuron. All of this calls for the development of new antipsychotics with different mechanisms of action.

This lecture provides a critical review of novel pharmacological approaches and the available clinical evidence. Particular attention is devoted to muscarinic agonists, primarily the combination of xanomeline–trospium. Its efficacy in short-term studies in acute schizophrenia has been confirmed, along with a different adverse-effect profile that is predominantly gastrointestinal and cholinergic. TAAR1 receptor agonists, modulators of glutamatergic neurotransmission (including glycine transporter inhibitors), and agents targeting serotonin receptors are also discussed.