Psychiatria Danubina, 2012; Vol. 24, Suppl. 3, pp 326–330 *Conference paper*

SEROTONERGIC ORGANIZATION OF THE CENTRAL NERVOUS SYSTEM

Ivana Timotijević[1], Žana Stanković[2], Mirjana Todorović[3], Srdjan Z. Marković[4] & Dragana A. Kastratović[5]

[1]*Euromedik, Medical Faculty University of Belgrade, Belgrade, Serbia*
[2]*Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, Serbia*
[3]*Section for Clinical Pharmacology, Serbian Medical Society, Belgrade, Serbia*
[4]*Medical Faculty University of Belgrade, Belgrade, Serbia*
[5]*Clinical Centre of Serbia, Belgrade, Serbia*

SUMMARY

The last 50 years of researches of biochemism and the CNS functionality are intensively engaged in studying the role of monoamine neurotramsmitter serotonin (5-hydroxytryptamin) (5-HT). The serotonergic receptors function depends on spot where the receptor function, the dynamic relationship with other transmitters and stimulation that can activate or inhibit specific neurons. The results of research in biochemistry, neurophysiology and neuroradiology have provided insight into the complexity of the operation of key structures such as the amygdala, prefrontal cortex and hippocampus, whose role varies depending on the received external impulses and the impulses that are sent to relevant areas. This implies that the transmitters and especially 5-HT, have much wider effects that are determined not to structures but by the impulse dynamics. It also means that psychopharmaceutical drugs whose therapeutic effect is based on the change of the concentration of serotonin in the synapse and the postsynaptic receptors depending on where they operate, have an effect on affective or cognitive symptoms. Serotonergic antidepressants by changing the concentration of serotonin change primarily affective manifestations but also they have significant influence on all the spectrum of serotonergic disorders not only emotional, but also the cognitive level, which is also a confirmation that the therapeutic effects do not depend only on the simple change of serotonin concentration but also of the level where these changes occur in dynamic comparison of key transmitters. Atypical antipsychotics which have low affinity for dopaminergic and high affinity for serotonergic receptors are seen through the dynamic relationship of serotonin, dopamine and noradrenalin in nigrostriatal, mezocortical, mezolimbic and tuberoinfudibular pathways.

Key words: *serotonin – receptors – hippocampus - amygdala nucleus*

* * * * *

INTRODUCTION

Serotonin (5-hydroxytryptamine) (5-HT) is a monoamine neurotransmitter. It was discovered in the year 1935 as an unknown substance, which has a role in the motility of the digestive tract, while his other roles in the body, especially in the central nervous system (CNS) were clarified later.

About 80% of 5-HT in the human body is synthesized in enterochromaphine intestinal cells, where regulates motility, and the part goes into the blood and platelets, which is released during clot formation and acts as vasoconstrictor. The rest is synthesized in neurons of raphe nuclei of reticular substance of CNS, whose projection ending in a number of lower and higher CNS structures, where as a neurotransmitter is involved in the transmission of impulses in the synapses and regulation of a variety of mental functions: mood, anxiety, sleep, appetite and cognition.

Biosynthesis of 5-HT occurs via the amino acid L-tryptophan, by action of two enzymes, tryptophan hydroxilase and amino acid decarboxylase, and decomposition action of the enzyme monoamine oxidase (MAO) and aldehyde dehydrogenase to the end products of 5 - hydroxyindolacetic acid (5-HIAA), which is excreted in urine (King 2009). In the CNS, synapses in the 5-HT neurons, 5-HT is discharged from the presynaptic vesicles of the cytoplasm of neurons in the synaptic cleft and activates 5-HT receptors located on the postsynaptic membrane, and partly to the presynaptic membrane. Most 5-HT receptors are of protein composition (except for 5-HT3 receptor, which is an ion channel) and activates a cascade of intracellular secondary messengers that triggers the exposure of genes and other complex molecular processes in nerve cells. The rest was returned to 5-HT neuron by action of the serotonin reuptake transporter (SERT) and recently discovered the plasma membrane monoamine transporter (PMAT) (Berger et al. 2009, Hannon & Hoyer 2008).

The effect of numerous psychopharmacologic (antidepressants, atypical antipsychotics) and non-psychopharmacologic substances (some antiemetics, antimigrenics) is achieved by modulating the action of serotonin synapses. Some pathogenic microorganisms (Entamoeba hystolitica) also act on serotonin (King 2009, Berger et al. 2009). Unwanted effects of some drugs or medical procedures are the result of the action on 5-HT receptors in different parts of the body (digestive tract, heart, bones), and the importance of serotonin is not restricted only in neuropsychopharmacology (Berger et al. 2009).

DEPRESSION SYPTOMS MAPPING, SEROTONERGIC SYSTEM AND ANTIDEPRESIVES ACTION MECHANISMS

Mood disorders in a wide spectrum of clinical manifestations in the light of biological etiological theories are associated with disturbances in the regulation of monoamine neurotransmitter systems in the CNS, 5-HT, noradrenaline (NA) and dopamine (DA) (Frazer & Hensler 1999).

It is understood that each of these disorders can be accessed symptomatic, and that every symptom hypothetically be related to disruption of the functioning of a certain part of the CNS, respectively one or more of the monoamine neurotransmitter systems. This leads to a deeper understanding of the concept of the pharmacological mechanism of action of drugs (antidepressants, and others), which are used in the treatment of affective disorders, as well as the possibility of individualization of treatment (adjustment of treatment of each patient and their specific symptoms) (Stahl 2008).

Both classification systems, ICD-X and DSM-IV (WHO 1994, American Psychiatric association 1994) have symptomatic-syndromic approach to diagnosis of depression and agree that the so-called. "core" symptoms are depressed mood and/or apathy or loss of pleasure and interest, with a range of additional symptoms such as sleep disturbance, appetite and body weight, cognitive functions, psychomotor activity, thought and will. All these symptoms can be mapped to specific regions of the CNS with specific monoamine neurotransmitter whose dysfunction induces specific symptoms (Caspi et al. 2003). This allows the selection of appropriate antidepressant, which would act in an appropriate neurotransmitter in the dysfunctional part of the CNS and thereby alleviate or relieve every single symptom of depressive disorder, or most of them, as well as effective and safe combination of two or more pharmacological agents in the treatment of severe forms of depression (Shin & Liberzon 2009). Typical depressive symptoms such as depressed mood, disturbed sleep and appetite, the idea of guilt, worthlessness and suicidal ideas are most associated with 5-HT neurotransmitter system. On the other hand, atypical cluster-apathy, loss of pleasure and interest, mental and physical fatigue and cognitive disorders are associated with NA and DA system (Stahl 2008, Gilbertson et al. 2002). Given that these are the most common residual symptoms of depression or symptoms that are resistant to treatment, in situations where they dominate the clinical picture, it is necessary to include antidepressants with predominant effect on NA and DA, or their combination with antidepressants with predominant effect on 5-HT in special cases (Stahl 2008).

Certainly, as a first-line drugs in the treatment of depressive disorders, as recommended by most of the famous guide to treatment, they are still these with the predominant effect on 5-HT, Selective serotonin re-uptake inhibitors (SSRI) (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram). These drugs are also used to treat anxiety disorders, eating disorders, premenstrual disphoric disorders and in preventing migraine attacks. Their action takes place mainly at 5-HT synapses, acting on SERT and selectively blocking of re-uptake mechanisms of 5-HT in presynaptic nerve endings. They act on 5-HT in the CNS and the periphery, and have also some other mechanisms of action, depending on the species, which is important both in applyment for the desired indication and the occurrence of adverse effects (Rich et al. 2009).

Combined therapy (the use of two antidepressants with different pharmacological profiles, or use of antidepressants with other psychoactive drugs) is associated with the interaction of applied drugs and the possibility of gain side effects. Pharmacokinetic interaction of fluvoxamine (SSRI) and tricyclic antidepressant amitriptyline (TCA), applied in combination in the treatment of major depressive disorder lead to reduced metabolism of amitriptyline. However, there were no significant effects of these interactions on the safety of treatment, and combined therapy had a rapid effect than monotherapy, according to our investigation (Vezmar et al. 2009). Concomitant therapy of major depressive disorder with moclobemide (antidepressant that increases extraneuronal concentration of neurotransmitters, especially serotonin (Reversible inhibitor of monoamine oxidase A)) (RIMA) and carbamazepine (a mood stabilizer), have followed by the increase in oral clearance of moclobemide, probably due to induction of metabolism of this antidepressant and its major metabolite (Rakic Ignjatovic et al. 2009). With combined use of drugs is necessary to take into account the possible dangerous combinations such as SSRI and monoamine oxidase inhibitors (MAOIs), which was the most common cause of most serious, potentially fatal adverse event, serotonin syndrome, which is characterized by alterations in mental status, neuromuscular abnormalities and autonomic dysfunction.

SEROTONERGIC-DOPAMINERGIC ANTAGONISM, THE PRINCIPLE OF ATYPICALITY AND SECOND-GENERATION ANTIPSYCHOTICS

The integrale DA hypothesis of schizophrenia (SCH) includes mesolymbic hyperactivity, associated with positive symptoms (paranoide ideas, hallucinations, agitation, hostility, conceptual disorganization), mesocortical hypoactivity associated with cognitive symptoms (dorsolateral prefrontal cortex-DLPFC; disorder of attention, concentration, executive functions),

negative symptoms (DLPFC and the ventromedial prefrontal cortex-VMPFC; aloga, avolicia, abulia, blunted affect, social withdrawal), and affective symptoms (VMPFC; depression, feeling of guilt, suicidality).

The function of nigrostrijatal (part of the extrapyramidal nervous system that controls motor function and movement) and tuberoinfundibular pathways (projections from the hypothalamus to the frontal part of the pituitary gland, which controls the secretion of prolactin) are unchanged.

Serotonergic system contributes to the development of psychotic states by interaction with other neurotransmitter systems in the brain. Serotonin regulates DA activity directly (via 5-HT1 receptors, whose stimulation increases the release of DA and 5-HT2 receptors, whose stimulation inhibits the release of DA), or indirectly, through gamma amino buteric acid (GABA) neurons. Interaction of 5-HT and DA at at the level of nigrostriatal pathways are important to reduce the incidence of extrapyramidal (EP) adverse effects of antipsychotics treatment (iatrogenic parkinsonism-rigidity, tremor, akinesia, tardive dyskinesia and tardive dystonia). Application of atypical antipsychotics (AA) is accompanied by a lower incidence of adverse effects of the EP. Contrary to conventional antipsychotics, the interaction of AA and D2 receptors is loose, resulting in rapid dissociation of the binding sites, a phenomenon known as "hit and run". The results of various preclinical and clinical studies have shown that 5-HT is closely associated with psychotic symptoms and mechanism of new atypical antipsychotics. For example, psihotomimetic psilocybin, which has no affinity for DA receptors, a partial agonist and several serotonin receptors have high affinity for 5-HT2A receptors. Glutamate neurotransmitter system is also involved in the modulation of DA activity. Hypoactivity of glutamate is associated with positive, negative, cognitive and affective symptoms of SCH (Stahl & Mignon 2010)

Second-generation antipsychotics (clozapine, olanzapine, quetiapine, risperidone, paliperidone, sertindole, ziprasidone) are potent 5-HT2A receptor antagonists and relatively weak D2 receptor antagonists (SDA) at clinically effective doses. They present newer drugs to improve therapeutic efficacy and reducing side effects. The effect on the level of 5-HT receptors contributes to a lower risk for extrapyramidal side effects, lack of hyperprolactinaemia (with the exception of risperidone and its major metabolite 9-hydroxi risperidone), an antipsychotic effect and the ability to repair certain domains of cognition in patients with SCH (Meltzer & Massey 2011). 5-HT3 receptors (only serotonin receptors linked to the opening of ion channels) play an important role in the modulation of inhibitory action of DA in mesocortical brain regions. Clozapine and olanzapine are 5-HT3 antagonists, which contributes to their therapeutic efficacy (Rammes et al. 2004).

AA achieve positive effects on cognitive function by 5-HT1A receptors stimulation and 5-HT6 and 5-HT7 receptors antagonism. In particular, 5-HT7 receptors antagonism may be grounds for procognitive effect of amisulpride, D2/D3 receptor antagonists, which are not linked to other 5-HT receptors. 5-HT2C receptor antagonism is associated with the effect on cognition and psychotic symptoms, through modulation of cortical and limbic DA activity. Antagonism at these receptors is associated with increased body weight, adverse effects, which usually occurs in the application of olanzapine and clozapine (Meltzer & Massey 2011). Ziprasidone, quetiapine and clozapine are also 5-HT1A partial agonists (SPA), and aripiprazole the SDA, SPA and D2 partial agonist (DPA). In addition to effects on receptors, zotepine and loxapine are NA re-uptake inhibitors (NRI), and ziprasidone is an NRI and 5-HT re-uptake inhibitor (SRI) (Stahl & Mignon 2010). The study of pharmacogenetic correlates of early response to antipsychotic treatment in patients with first- episode SCH, which were not previously treated, 5-HT 2C polymorphism was associated with a reduction in symptom severity, as a result of the effects on negative and general symptoms, but not positive symptoms. D3 genotype was also associated with a reduction in symptom severity, as a result of the effects on positive and general symptoms, but not negative symptoms (Reynolds et al.2005).

The results of some studies suggest moderate efficacy of amisulpride in lower doses in the treatment of primary negative symptoms of SCH. Selective serotonin re-uptake inhibitors (SSRIs) and mirtazapine (Noradrenergic and specific serotonergic antidepressant) (NASS) and N-methyl-d-aspartate (NMDA) agonists are promising, but require further study (Murphy et al. 2006).

Heterogeneity of clinical manifestations of SCH is complicated by the presence of psychiatric comorbidity such as anxiety disorders and depression. Anxiety and depressive symptoms may occur in the prodromal phase, acute phase and post-psychotic stage. Antipsychotic treatment may lead to a primary dysphoria, probably due to DA blockade in the CNS structures that are associated with the principle of pleasure and reward (reward pathways). Differential diagnosis of depression in these patients include neurologic side effects of antipsychotics (parkinsonism, akathisia), and negative symptoms (abulia, alogia, anhedonia, blunted affect). AA (olanzapine, clozapine in reducing suicidality) have proven efficacy in the treatment of depressive symptoms in SCH patients (Nemeroff 2005). AA as it has been found effective in the treatment of resistant forms of unipolar and bipolar depression. AA as a potent 5-HT2 antagonists in low doses, can facilitate the action of serotonin at 5-HT1A receptors and thereby increase the effectiveness of SSRIs. Pharmacological profile of AA include some other effects, important for the treatment of depression, such as α2 antagonism (risperidone), 5-HT1 agonism (ziprasidone and aripiprazole) and NA and 5-HT re-uptake inhibition (ziprasidone). AA Olanzapine and risperidone are used as adjuvant therapy in the treatment

of anxiety disorders (obsessive-compulsive and generalized anxiety disorders) (Hamilton & Malone 2000).

There is evidence that other serotonin receptor antagonists, except for 5-HT1A, especially the 5-HT2 and 5-HT3, such as risperidone and ondansetron, may precipitate serotonin syndrome. There are rare presentations of association of serotonin syndrome and atypical antipsychotic therapy (Duggal & Fetchko 2002, Trollor et al. 2009). Neuroleptic malignant syndrome (NMS) (a combination of hyperthermia, rigidity, and autonomic dysregulation), a rare side effect of antipsychotic therapy, with the possibility of lethal outcome, can occur with the newer AA (olanzapine, risperidone, paliperidone, aripiprazole, ziprasidone, amisulpride, quetiapine and clozapine) (Garcia-Cabeza et al. 2001).

According to the results of several studies (Dolder et al. 2002, Perkins et al. 2006, Geddes et al. 2000), therapeutic adherence in patients on treatment with AA is better than in those on conventional antipsychotics, and possible explanations are differences in efficacy and tolerability (Geddes et al. 2000). In addition, the greater the possibility of a positive subjective response in the patients who were treated with AA (Dolder et al. 2002). There are also studies that have not confirmed the previous results (Gilmer et al. 2004, Freudenreich et al. 2004, Stankovic et al. 2008, Jakovljevic et al. 1991). The results of studies conducted in our patient population, suggest that special attention should be focused on the attitudes, severity of psychopathology, insight into the illness, and history of non-compliance with treatment in the assessment of compliance in SCH patients on post-hospital treatment (Jakovljevic et al. 1991).

CONCLUSION

Accumulation of data on serotonergic organization and function of the Central Nervous System in healthy and morbid conditions has largely improved the understanding of etiopathogenesis of the affective and cognitive disorders. Concurrently, therapeutic approach has become more selective, specific and efficient, yet not more causal.

Synaptic transmission proceeds via presynaptic and postsynaptic receptor activation resulting in the change of the amount of released transmitters. Consequently, the processes of postsynaptic impulse modulation take place in postsynaptic neuron as well as the processes of genome modifications. The function of serotonergic receptors and psychopathological equivalents are conditioned by the respective CNS structures in which they function (prefrontal cortex, amygdaloid complex, hippocampus and hypothalamus). Serotonin is a neurotransmitter connecting the receptors, structures and behavioral manifestations in psychiatric disorders.

The symptoms of most frequent psychiatric disorders, depression and schizophrenia, are presented in both entities and treated by the same medicaments (new generation antidepressants and second-generation antipsychotics), because their mechanisms of action share the same receptors and appropriate CNS structures. A new approach to treatment of psychiatric symptoms implies a new map of morbigenous processes and specific drug utilization, individualized for each patient with consideration of genotypical and phenoltypical expression in specific structures and dynamics of receptors involved in etiopathogenesis of depression and schizophrenia.

Acknowledgements: None.

Conflict of interest: None to declare.

REFERENCES

1. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV). Washington, DC: American Psychiatric Press, 1994.*
2. *Berger M, Gray JA, Roth BL. The expanded biology of serotonin. In: Annu. Rev. Med 2009; 60:355-66.*
3. *Caspi A, Sugden K, Moffit TE et al. Influence of life stress on depression: moderation by a polymorphizm in the 5-HTT gene. Science 2003; 301:195-216.*
4. *Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002; 159:103-8.*
5. *Duggal HS & Fetchko J. Serotonin Syndrome and Atypical Antipsychotics. Am J Psychiatry 2002; 159:672-3.*
6. *Frazer A & Hensler JG. Understanding the neuroanatomical organizacion of serotonergic cells in the brain provides insight into the functions of this neurotransmitter. In Sigel GJ. Basic Neurochemistry 1999; 212-24.*
7. *Freudenreich O, Cather C, Evins AE, Hendersin DC, Goff DC. Attitudes of schizophrenic outpatients toward psychiatric medication: relationship to clinical variables and insight. J Clin Psychiatry 2004; 65(10): 1372-6.*
8. *Garcia-Cabeza I, Gomez JC, Sacristan JA, Edgell E, Gonzalez de Chavez M. Subjective response to antipsychotic treatment and compliance in schizophrenia. A naturalistic study comparing olanzapine, risperidone and haloperidol (EFESO Study). BMC Psychiatry 2001; 1:7.*
9. *Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000; 321:1371-6.*
10. *Gilbertson MW, Shenton ME, Ciszewatski A. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. Nat Neurosci 2002; 5(11):1242-7.*
11. *Gilmer TP, Dolder R., Lacro JP, Folsom P, Lindamer L, Garcia P, et al. Adherence to Treatment With Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries With Schizophrenia. Am J Psychiatry 2004; 161: 692-9.*
12. *Hamilton S & Malone K. Serotonin syndrome treatment with paroxetine and risperidone (letter). J Clin Psychopharmacol 2000; 20:103-5.*
13. *Hannon J & Hoyer D. Molecular biology of 5-HT receptors. Behavior Brain Res 2008; 195:198-213.*

14. Jakovljevic M, Muck-Seler D, Kenfelj H, Plavsis V, Biocina S, Kastratovic D, Ljubicic Dj. Basal cortisol, dexamethasone suppression test and platelet 5-HT in recurrent (unipolar) major depression, schizophrenia and schizoaffective disorder. Psychiatr Danub 1991; 3:389-414.
15. King MW. Serotonin. The Medical Byochemistry Page Indiana University School of Medicine 2009; 12–01.
16. Meltzer HY & Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Current Opinion in Pharmacology 2011; 11:59-67.
17. Murphy BP, Chung YC, Park TW, McGorry PD. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res 2006; 88:5-25.
18. Nemeroff CB. Use of Atypical Antipsychotics in Refractory Depression and Anxiety J Clin Psychiatry 2005; 66:13-21.
19. Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006; 83:53-63.
20. Rakic Ignjatovic A, Miljkovic B, Todorovic D, Timotijevic I, Pokrajac M. Moclobemide monotherapy vs. combined therapy with valproic acid or carbamazepine in depressive patients: a pharmacokinetic interaction study. Br J Clin Pharmacol 2009; 67:199-208.
21. Rammes G, Eisensamer B, Ferrari U, Shapa M, Gimpl G, Gilling K et al. Antipsychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner. Mol Psychiatry 2004; 9:846-58.
22. Reynolds GP, Yao Z, Zhang X, Sun J, Zhang Z. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. Eur Neuropsychopharmacol 2005; 15:143-51.
23. Rich N, Herrel R, Lehner T et al. Interaction between the serotonin transporter gene (5-HTTLPR), stresful life events and risk of depression: a meta-analysis. JAMA 2009; 301:2462-71.
24. Shin LM & Liberzon I. The neurocircitry of fear, stress, and anxiety disorder. Neuropsychopharmacol 2009; 66:658–65.
25. Stahl SM & Mignon L. Neurobyology of Schizophrenia and Mood Disorders. In: Stahl SM, Mignon L, editors. Stahl's Illustrated Antipsychotics: Treating Psychosis, Mania and Depression (2nd edition). Cambridge University Press, Cambridge/New York; 2010; p.1–30.
26. Stahl SM. Stahl's essential psychopharmacology, Third edition. New York, NY: Cambrige University Press; 2008.
27. Stanković Ž, Britvić D, Vuković O, Ille T. Treatment compliance of outpatients with schizophrenia: patient's attitude, demographic, clinical and therapeutic variables. Psychiatria Danubina 2008; 20:49-59.
28. Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS Drugs 2009; 23:477-92.
29. Vezmar S, Miljkovic B, Vucicevic K, Timotijevic I, Prostran M, Todorovic Z, et al. Pharmacokinetics and efficacy of fluvoxamine and amitriptyline in depression. J Pharmacol Sci 2009; 110:98-104.
30. World Health Organization. International Classification of Diseases, 10th edn (ICD-10). Geneva: WHO, 1994.

Correspondence:

Prof. Dr. Ivana Timotijević, MD, PhD
Medical Faculty University of Belgrade, Euromedik
Alekse Nenadovića 7, 11000 Belgrade, Serbia
E-mail: vanja.timotijevic@gmail.com