Current Treatment of Schizoaffective Disorder According to a Neural Network

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**Abstract**

Schizoaffective disorder, which is combined with schizophrenic and affective, i.e. depressive or manic or alternating depressive and manic symptoms, has a prevalence of 0.5%. Here, we describe the alterations of the most important classical neurotransmitters in the brain regions involved in schizophrenic and affective symptoms. Schizoaffective is undoubtedly an inheritable chronic psychiatric disease, whereby trauma may enhance schizophrenic and affective symptoms in one third of patients. Neural networks are described in the brainstem, hippocampus and ventral tegmental area and the mentioned neurotransmitter alterations are considered. Prophylactic treatment of schizoaffective patients consists of administering mostly second-generation antipsychotic drugs alone or in combination with mood-stabilizing drugs. The clinical importance of the antipsychotic drug clozapine for a pharmacotherapy of treatment-resistant forms of the disease is underlined.

**Keywords**: Clozapine; Dopamine; Extrapyramidal symptoms; GABA; Glutamate; Lithium; Mood-stabilizing drug; Noradrenaline; Olanzapine; Quetiapine; Risperidone; Second-generation antipsychotic drug; Serotonin

**Introduction**

While schizophrenia, a chronic disabling psychiatric disease, affects 1% of the population, the schizoaffective disorder has a prevalence of 0.5%. Schizoaffective patients show positive schizophrenic symptoms (paranoia, hallucinations, illusions), negative schizophrenic symptoms (social withdrawal, autism, mutism) and cognitive deficits. Schizophrenic symptoms are combined with affective, i.e. depressive, manic or bipolar symptoms. Schizoaffective disorder becomes manifest as an acute psychosis with mostly positive schizophrenic and depressive or manic symptoms [1-3]. The brain regions involved in schizophrenic symptoms are the hippocampus, the prefrontal cortex and the ventral tegmental area. In these brain regions, dopamine hyperactivity via D2 receptors and serotonin hyperactivity via 5-HT1A receptors occur. Besides, an hypoactivity of presynaptic inhibitory neurons, namely GABAergic neurons via GABA_A receptors and glutamatergic neurons via NMDA (N-methyl-D-aspartate) neurons, has been reported. Dopamine hyperactivity and GABA and glutamate dysfunction is encoded by the susceptibility genes of the schizophrenic symptoms [4]. The brain regions involved in affective symptoms are the hippocampus and the brain stem. In these brain regions, hypoactivity of monoamines, namely noradrenaline, serotonin and dopamine neurons and hyperactivity of presynaptic inhibitory neurons, i.e. GABAergic and glutamatergic neurons can be found [5,6]. 30% of the schizoaffective patients experienced traumata and this enhanced the disease symptoms [7]. Schizoaffective disorder is treated generally with second-generation antipsychotic drugs such as risperidone, olanzapine, quetiapine or aripiprazole. The antipsychotic drugs are mostly D2 and 5-HT1A antagonists and improve positive and negative schizophrenic symptoms [8]. Additionally, mood-stabilizing drugs such as lithium, carbamazepine or lamotrigine can be administered in order to prevent recurrence of psychotic or affective symptoms [9].

**Alterations of Classical Neurotransmitters and Neuropeptides in the Brain Regions Involved in Schizophrenic Symptoms**

The brain regions involved in schizophrenic symptoms are the hippocampus, the prefrontal cortex and the ventral tegmental area [3]. After the description of some susceptibility genes related with the schizophrenic symptoms and the coherence between genetic localization and cellular mechanisms [10], a multi-neurotransmitter system has been also described in the above mentioned brain regions. In the ventral tegmental area, dopamine hyperactivity via D2 receptors and serotonin hyperactivity via 5-HT1A receptors have been described, while dopamine hyperactivity was due to a reduced activity of the enzymes degrading dopamine, namely COMT (catechol-O-methyl transferase) and monoamine oxidase. Presynaptic inhibitory neurons are also important and it is known that GABA hypoactivity, via GABA_A receptors, is encoded in the GAD (glutamic acid decarboxylase)-67 gene and glutamate hypoactivity, via NMDA receptors, in the dysbindin-1 and neuregulin-1 genes [11]. Some neuropeptides are also involved in psychotic symptoms, for example in the prefrontal cortex, decreased levels of cholecystokinin and neurotensin have been reported [12].

**Dopamine**

In schizophrenia and in the schizoaffective disorder, a dopamine hyperactivity via D2 receptors has been described in the hippocampus, the prefrontal cortex and the ventral tegmental area. Dopamine hyperactivity is enhanced by a reduced activity of two enzymes degrading dopamine, namely COMT and monoamine oxidase [12]. In the section about the neural networks, it will be pointed that in the ventral tegmental area GABAergic neurons, due to the gene GAD 67, exert a weak presynaptic inhibitory action on D2 dopaminergic neurons and enhance dopamine hyperactivity. Although the antipsychotic drug

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clozapine (a D2, D3, and 5-HT1A antagonist) exerts an antipsychotic effect higher to other antipsychotic drugs, the D3 antagonistic effect is of great importance in the treatment of schizophrenic symptoms [13].

**Serotonin**

Serotonin hyperactivity via 5-HT1A receptors can be found in the hippocampus and the ventral tegmental area. In animal experiments, NMDA receptor antagonists, for example MK-801 can induce schizophrenia-like behavior which can be relieved by risperidone, a D2 and 5-HT1A antagonist and ritalinserin, a 5-HT1A and 5-HT2C receptor antagonist, but not by haloperidol, a D2 antagonist [14]. In the section about neural networks, it will be pointed out that glutaminergic neurons exert a reduced presynaptic inhibitory function, via NMDA receptor, on 5-HT1A serotonergic neurons in the hippocampus and ventral tegmental area and enhance serotonin hyperactivity [3].

**Gamma-aminobutyric acid (GABA)**

GABA is a presynaptic inhibitory neurotransmitter, which exerts its function via GABA_A and GABA_B receptors. In schizophrenia and schizoaffective patients, GABA is dysfunctional in the hippocampus, prefrontal cortex and ventral tegmental [15]. In these brain regions, it has been reported reduced levels of GAD 67 mRNA and GAD protein in the prefrontal cortex of schizophrenic patients [16]. GABAergic neurons could enhance D2 dopamine hyperactivity through a decreased presynaptic inhibition via GABA_A receptors [12].

**Glutamate**

Glutamate is dysfunctional in the brain regions in schizophrenic brain regions due to the susceptibility genes dysbindin-1 and neuregulin-1, which encode glutamate hypoactivity via the NMDA receptor in the prefrontal cortex, hippocampus and ventral tegmental area. It has been examined whether a positive allosteric modulator at the NMDA receptor might be of therapeutic effect in schizophrenia and schizoaffective disorder [17].

**Alterations of Classical Neurotransmitters and Neuropeptides in the Brain Regions Involved in Affective Symptoms**

Schizoaffective patients show schizophrenic symptoms accompanied by affective symptoms, i.e. depressive, manic or bipolar, alternating depressant and manic symptoms. The brain regions involved in the affective symptoms are the brainstem and hippocampus. In patients showing depressive symptoms, hypoactivity of monoamines, i.e. of dopamine, noradrenaline and serotonin can be found respectively in the brainstem and hippocampus. In addition to the hypoactivity of these postsynaptic excitatory neurotransmitters, hyperactivity of the presynaptic inhibitory neurotransmitters GABA and glutamate can be found. In patients showing manic symptoms, hyperactivity of dopamine and serotonin and hypoactivity of the presynaptic inhibitory neurotransmitters GABA and glutamate occurs. A neural network will be developed in order to explain the interactions between these neuroactive substances in a multineurotransmitter system (Figure 1) [12].

**Noradrenaline**

In depressive and manic symptoms, noradrenaline alterations are of importance in the midbrain and hippocampus. In depressive patients, hypoactivity of noradrenaline via alpha1 receptors is partly due to polymorphisms of the noradrenaline transporter gene. Patients with polymorphisms of this gene better respond to selective noradrenaline and serotonin reuptake inhibitors than to selective serotonin reuptake inhibitors [18].

**Serotonin**

Serotonin hypoactivity in the brainstem and hippocampus can be found in depressive patients; this serotonin alteration is partly due to polymorphisms of the serotonin transporter gene. Selective serotonin reuptake inhibitors improve depressive symptoms; this effect being combined with an antagonism at other serotonin receptors, namely 5-HT2C and 5-HT2 receptors [19].

**Dopamine**

In the hippocampus, dopamine shows hypoactivity in schizodepressive patients and hyperactivity in schizomani patients. In depressive patients, the selective dopamine and noradrenaline reuptake inhibitor bupropion improves the decreased positive effect, i.e. the loss of interest, pleasure and interest. However, in schizodepressive patients, the antidepressant drug bupropion should not be administered, because bupropion can enhance dopamine hyperactivity and worsen manic or schizophrenic symptoms, when they occur.

**Gamma-aminobutyric acid (GABA)**

GABA shows dysfunction in depressive and manic symptoms in the brainstem and hippocampus. In the brainstem, GABAergic neurons strongly presynaptically inhibit alpha1 noradrenergic neurons, via GABA_A receptors, and contribute to noradrenaline hyperactivity in depressive symptoms [20,21]. In schizomani patients, in the hippocampus, GABAergic neurons weakly presynaptically inhibit D2 dopaminergic neurons via GABA_A receptors [4].

**Glutamate**

In schizodepressive and schizomani patients, glutamate shows respectively hypo- and hyper-activity in the brainstem and hippocampus. In the brainstem, glutamatergic neurons strongly presynaptically inhibit 5-HT1A serotonergic neurons via subtype 5 of metabotropic glutamatergic receptors (m5GluRs) and enhance serotonin hypoactivity [12]. NMDA receptor and m5Glu receptor antagonists exert an antidepressant effect. However, in schizodepressive patients, these novel antidepressant drugs should not be administered, because in the hippocampus and ventral tegmental area, an antagonism at the NMDA receptor could enhance 5-HT1A serotonin hyperactivity through a reduced presynaptic inhibition, enhancing psychotic symptoms [22].

**Neural Networks in the Brain Regions Involved in Schizophrenic and Affective Symptoms**

Neural networks in the brainstem, hippocampus and ventral tegmental area can be described as follows: In the brainstem, alpha1 noradrenergic neurons, originating from the locus coeruleus activate glutamatergic neurons, which inhibit 5-HT1A serotonergic neurons from the medial raphe nucleus, via NMDA receptors. The latter neurons activate GABAergic neurons, which inhibit alpha1 noradrenergic neurons via GABA_A receptors. This neural circuit is located in the center of the circadian rhythm; in this circuit, alternating levels of the activating neurotransmitter noradrenaline and the soothing neurotransmitter serotonin influence each other. Noradrenaline is preponderant during the day and serotonin during the night (Werner and Covenas). Alpha1 noradrenergic neurons activate glutamatergic neurons which inhibit 5-HT1A serotonergic neurons from the dorsal raphe nucleus via 5Glu
receptors. The latter neurons activate GABAergic neurons, which inhibit alpha1 noradrenergic neurons via GABA$_A$ receptors. This neural circuit could be named "mood center". As consequence of the reciprocal influence of the described neurotransmitters upon each other, an increased presynaptic glutamatergic inhibition of 5-HT$_{1A}$ serotonergic neurons, via m5Glu receptors, enhances serotonin hypoactivity and hyperactivity of presynaptic GABAergic neurons, via GABA$_A$ receptors, enhances noradrenaline hypoactivity. These neurotransmitter alterations could be associated with depressive symptoms. GABAergic neurons of the "mood center" inhibit other GABAergic neurons of the center for the circadian rhythm, via GABA$_A$ receptors, and glutamatergic neurons from the "mood center" inhibit other glutamatergic neurons of the center for the circadian rhythm, via m5Glu receptors [12]. In the hippocampus, D$_2$ dopaminergic neurons activate glutamatergic neurons which presynaptically inhibit 5-HT$_{1A}$ neurons, via NMDA receptors. The latter neurons activate GABAergic neurons which presynaptically inhibit, via GABA$_A$ receptors, D$_2$ dopaminergic neurons. Glutamatergic neurons from the hippocampus inhibit 5-HT$_{1A}$ serotonergic neurons in the brainstem, and GABAergic neurons from the hippocampus inhibit alpha1 noradrenergic neurons in the brainstem [4].

In the ventral tegmental area, in schizophrenia and schizoaffective
Lithium

Lithium is a mood-stabilizing drug with a therapeutic effect on affective symptoms. One third of the patients treated with lithium have no recurrence of affective symptoms. It decreases the excitatory effect of dopamine and glutamate and increases the presynaptic inhibitory effect of GABA. The main adverse effects are cardio- and nephro-toxicity [27].

Carbamazepine

Carbamazepine is an antiepileptic drug and a mood-stabilizing drug. It blocks fast-inactivated sodium channels. A combination of SGAs with carbamazepine has comparable therapeutic effect in schizoaffective patients like the administration of SGAs alone [28].

Lamotrigine

Lamotrigine is an antiepileptic drug and a mood-stabilizing drug. It blocks voltage-gated sodium channels and alpha4beta2 nicotinic cholinergic receptors and stabilizes dopaminergic neurons. In meta-analyses, it has been shown than lamotrigine combined with clozapine can treat successfully clozapine-resistant forms of schizophrenia and schizoaffective disorder [29].

Conclusion

Schizoaffective disorder, a chronic psychiatric disease, with schizophrenic and affective symptoms has a prevalence of 0.5% in the population. Susceptibility genes which encode dopamine hyperactivity and GABA and glutamate dysfunction have been discovered. In one third of the patients, traumatic enhancement alterations of classical neurotransmitters. Neurone transmitter alterations in schizoaffective and depressive symptoms have been described, while dopamine, noradrenaline and serotonin are postsynaptic excitatory neurotransmitters and GABA and glutamate presynaptic inhibitory neurotransmitters. Neural networks are described in the brainstem, hippocampus and ventral tegmental area, in which the coherence between the function of the susceptibility genes and the cellular mechanism is considered. The current pharmacotherapy of schizoaffective patients consists in administering second-generation antipsychotic drugs, for example risperidone, olanzapine, quetiapine or clozapine alone or in combination with mood-stabilizing drugs. Among the latter drugs, lithium can prevent recurrence of affective symptoms in one third of patients. In order to improve patients’ adherence to the pharmacotherapy, it is important to combine this therapy with social integration and psychoeducation.

References


