

Cognitive Dysfunction and Its Therapy – Challenge for the 21st Century

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SUMMARY

Firstly, the meaning of the terms cognition and cognitive dysfunction is clarified. Cognitive dysfunction is found in many neuropsychiatric disorders. Most studies have been performed in patients with schizophrenia and dementia. For the purposes of studying cognitive dysfunction, the initial phases of diseases are the most suitable. Then the opportunities for treating cognitive dysfunction in schizophrenia are summarized. Atypical antipsychotics represent the basal treatment. The improvement of cognitive deficit achieved by the use of atypical antipsychotics is significant, but the importance of this in real life is small. The new add-on treatment has the potential for further improvement of cognitive dysfunction. This approach includes augmentation of neurotransmitters connected with cognition (glutamate, noradrenaline, serotonin, acetylcholine). The improvement of cognitive dysfunction can improve the long-term outcome and functional prognosis in patients suffering from schizophrenic disorder.

Key words: cognitive dysfunction, schizophrenia, dementia, atypical antipsychotics, add-on treatment, augmentation.

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Improvement of symptoms of a disease is necessary for the evidence of clinical efficacy in medicine. However, for the therapy to be really effective, it is necessary for the patient to be able to live independent of other people's help, to communicate with the surroundings and to find employment. Cognitive functions are a key factor that determines the ability to function in various areas (social, occupational). Especially in mentally ill people, disturbance of cognitive functions, i. e. cognitive dysfunction, is one of the main reasons why the patients cannot adequately integrate into normal life (1).

COGNITIVE DYSFUNCTION

Cognitive function consists of many individual components measurable by neuropsychological tests: speed of information processing, verbal learning, verbal memory, visual learning and visual memory, working memory, attention (a complex function influencing the others), executive function (initiating, planning and problem-solving), social cognition.

A neuropsychological examination is a special investigation aiming to determine whether the symptoms of brain impairment are present in a person's behavior and experience, and what form these symptoms take. It is based on special tests developed over a long period for the purpose of sensitive assessment of the relationship between brain and behavior. They evaluate qualitatively and quantitatively cognitive dysfunction, efficiency potential, and premorbid level of psychics, and they are able to help localize the damage.

Cognitive dysfunction may be found in many neuropsychical diseases, mainly in schizophrenia, depression, dementia, cerebrovascular impairment, seizure disorders, parkinsonism and head

injury. There are specificities of the individual disturbances (dynamics, influenceability) and also many resemblances (anatomical substrate, treatment). Attention has mostly been focused on the connection between schizophrenic disturbance and dementia. It is linked with particular anatomical and functional substrate (hippocampus, prefrontal cortex) and closely associated with functional prognosis.

Cognitive dysfunction in schizophrenia

This is considered a core symptom, responsible for social maladaptation after subsiding positive symptoms. It is linked with negative symptoms and with subtle structural and functional abnormalities in the central nervous system (CNS). In particular, attention is impaired, as are memory - including working memory (ability to store information "on line" and use it for processing) - and executive functions. Cognitive dysfunction may be detected before the onset of the disease. Despite its relative stability, it is characterized by certain dynamics. It may deteriorate in some patients, get worse during exacerbation, and fail to return to the premorbid level during remission (only 15% of patients return to the level of healthy people, clinically significant dysfunction occurs in 40–60%). Some components of cognitive functions, though still impaired in comparison with controls, get better in the course of treatment, mainly in the initial phase of the disease. Therefore special attention is paid to the first episodes of schizophrenia. It has been ascertained (and is confirmed by our experience) that the patients who continue with maintenance treatment with an antipsychotic that is effective in the acute phase, show improvement of cognitive dysfunction during long-term follow-up (2-6).

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On the basis of an initiative by American neuroscientists, project MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) was launched, aiming to stimulate the development of novel drugs for cognitive deficit, including establishment of therapeutical units specialized in the treatment and research of cognition in schizophrenia (7).

Cognitive dysfunction in dementia

This is a leading symptom with progressive memory disorders which finally influence all other psychical functions and, in conclusion, lead to institutionalization.

Cognitive dysfunction in depression

To a certain extent, this is connected with motivation: some studies indicate that cognitive deficit improves together with regression of depressive symptoms (6).

PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIC DISORDER

Many studies have dealt with the problem, and a high-quality summary has also been published in the Czech literature (8). Most studies have been aimed at schizophrenia and dementia.

The possibilities of pharmacological influencing of cognitive deficit in schizophrenia may be divided into two groups:

1. atypical antipsychotics (APs),
2. augmentation, i. e. add-on treatment, whose efficacy is based on the presumption that the activity of individual neurotransmitters is insufficient in some regions of CNS (ascending tracts projecting into prefrontal cortex are mentioned most often), and that strengthening them may contribute to amelioration of cognitive dysfunction. Augmentation approaches are also used for treatment of cognitive deficit in other nosological units.

Atypical antipsychotics (APs)

The prevailing view at present is that atypical APs, in addition to the treatment of schizophrenic symptoms, also have the potential to favorably influence cognitive dysfunction. At the beginning of the psychopharmacological era in the 1950s, attention was paid mainly to the positive symptoms (e. g. psychotic symptoms, delusions, hallucinations). Later, with the onset of atypical APs, interest shifted also to the negative symptoms and their treatment. Recently, emphasis has been placed on therapy of cognitive dysfunction.

Classical APs, also called first generation atypical antipsychotics (chlorpromazine, haloperidol), mainly improve the positive symptoms; they may actually worsen negative symptoms, and they do not markedly influence cognitive dysfunction. They are burdened with adverse neurological symptoms, increase body weight and prolactin levels. Atypical APs, APs of the second generation (amisulpride, risperidone, ziprasidone, clozapine, olanzapine, quetiapine, aripiprazole) may improve the positive and negative symptoms and cognitive dysfunction. Prevailing adverse reactions are metabolic adverse effects, i. e. body weight gain and impairment of glucose and lipid metabolism; some of them also increase prolactin (amisulpride, risperidone).

Mutual comparison of atypical APs showed improvement in a broad spectrum of cognitive domains, while significant differences between single atypical APs were found within influencing of attention and verbal fluency (9). In chronic patients, the results of comparison of atypical and typical APs are not entirely consistent, in contrast with the first episodes, in which atypical APs are unequivocally more convenient (10-13). At the first manifestation of psychotic symptomatology, marked worsening of cognitive dys-

function may develop. On the other hand, however, in the cooperating responders to the treatment this deficit may be ameliorated (6, 13). These results indicate the importance of selecting atypical APs and ensuring compliance in this subpopulation of mentally ill persons.

Among the many mechanisms leading to the positive influence on cognitive dysfunction by atypical APs, the main ones are increased availability of dopamine (DA) and acetylcholine (ACh) in the prefrontal cortex and hippocampus. These two neurotransmitters and two brain areas are obviously most closely connected with cognition. Other possible mechanisms include partial agonisms of dopamine receptors of D₂ type (in aripiprazole and bupropion), blockade of some types of serotonin receptors (5-HT_{2A}, or eventually agonism of 5HT₁ receptors) and modulation of glutamatergic system.

Augmentation – accessory treatment

Glutamatergic augmentation strategies

Excitatory amino acids (glutamate, aspartate, homocystein) are the most common neurotransmitters in the brain, and they are important for mechanisms of memory and learning. This strategy is based on hypothesis about lowered activity of NMDA (N-methyl-D-aspartate) receptors in schizophrenic disorder, which is linked to negative symptoms and cognitive dysfunction. The direct agonists could be dangerous; therefore modulation at the glycine site is used. The latest controlled study, comparing the influence of augmentation of antipsychotics with D-cycloserine to a placebo, showed the disadvantage of glutamatergic augmentation (14). Partial inhibitors of NMDA receptors (N-methyl-D-aspartate) are among the other potential candidates. The only compound accessible in practice is memantine (Ebixa). Memantine is well tolerated, the indication applied currently is moderate or severe Alzheimer's disease, and it is often used in combination with cholinesterase inhibitors. Modulation of AMPA receptors with ampakines and inhibition of selective glycine reuptake (sarcosine) also seems promising (15).

Modulation of serotonin (5-HT) receptors

Serotonin pathways originating from raphe nuclei project into all regions connected with cognition, being in mutual anatomical and functional interaction with other neurotransmitters (DA, ACh, glutamate). On the basis of a review of preclinical and clinical studies, it can be said that 5HT_{1A} partial agonists (e. g. tandospirone), 5-HT₂ antagonists, 5-HT₄ partial agonists (so far not tested in humans) and 5-HT₆ antagonists (in the phase of clinical testing) may lead to mild improvement of cognition in schizophrenia.

Atypical APs as a whole are characterized by mild 5-HT₁ agonistic effect (aripiprazole, olanzapine, clozapine, ziprasidone, quetiapine), by 5-HT₂ antagonism (with exception of amisulpride and aripiprazole) and by the different level of 5-HT₆ antagonism. That is why it is suitable to choose for augmentation strategy such APs that do not influence the respective 5-HT receptors (16).

Noradrenergic augmentation

Noradrenergic projection from locus coeruleus to the prefrontal cortex is connected with cognitive functions. The noradrenergic system can be augmented by administering alpha 2-selective agonists (guanfacine). Another possibility is the administration of specific noradrenaline reuptake inhibitors (NRI – atomoxetine or reboxetine) and of specific noradrenaline and dopamine reuptake inhibitors (NDRI – bupropion), which have recently been used as antidepressants (17). For the time being, the research of cognitive dysfunction in depression is a new challenge, and the influence of these antidepressants, preferentially increasing accessibility of noradrenaline (NA), on the cognition, has only been investigated exceptionally in depressive disorder. In general, noradrenaline is

attributed to activation function and its decrease is connected with fatigue, apatia, anhedonia, lack of initiative, lack of concentration, and inefficiency. DA is a neurotransmitter of the reward system, and the alteration is connected with problems in sexual areas, appetite disorders, lack of interest, lack of motivation, and lack of attention (18, 19). NA and DA are in very close relation – NA is created by biodegradation of DA with the dopamin beta hydroxylase. It is interesting that in addition to depression, the target disorder for NDRI (or NRI) is also ADHD (attention-deficit/hyperactivity disorder) – another disorder in which cognitive dysfunction plays a role. Of the NDRI group, the only preparation available in this country is bupropion. The stimulants nonselectively releasing NA may lead to exacerbation of psychosis. Centrally active inhibitors of catechol-O-methyltransferase (COMT) may well also be effective.

CHOLINERGIC POTENTIATION - COGNITION ENHANCERS

The central Ach system is important for memory (short-term memory, imprinting capacity). Cholinergic potentiation is well-developed in dementias in which lowered activity of acetylcholinesterase is consistently found. The term cognition enhancers - smart drugs - is used for the drugs that increase accessibility of Ach in CNS by means of various mechanisms: 1. Delivery of precursors of Ach generation (e. g. lecithin, though this is not effective with respect of poor passage through blood-brain barrier). 2. Inhibition of cholinesterases (i. e. enzymes degrading acetylcholine) – for the present, the most important mechanism. 3. Antagonistic activity on appropriate receptors, i. e. muscarinic and nicotinic receptors. So far, the central inhibitors of cholinesterases have been the most effective known therapy in mild and moderate form of Alzheimer's dementia (AD) and Lewy body dementia. The efficacy is verified in other types of dementia. The main effect of cholinesterase inhibitors is slowing down the course of the disease, postponement of the transition into the severe stage of the disease. In a portion of treated patients, contemporary improvement of cognitive functions, disorders of behavior, activities of everyday life and emotivity is achieved. In this country, donepezile (Aricept), galantamine (Reminyl) and rivastigmine (Exelon) are accessible.

Inhibitors of acetylcholinesterase have also been tested in cognitive deficit in schizophrenia (donepezile and galantamine). The published studies, including studies by these authors, show that rather than donepezile, galantamine may well be successful, because in addition to inhibition of acetylcholinesterase, it also potentiates the nicotinic receptors (20, 21). In schizophrenia, a reduced number of muscarinic and nicotinic receptors in cortex and hippocampus is found; patients with schizophrenia are far more often heavy smokers (70–80%) opposed to normal population (25–30%).

THE FUTURE

So called “memory enhancers” are among promising molecular therapeutical targets. In particular, these include CREB activators (cAMP response element binding protein), that increase growth of synapses, thus positively influencing the plasticity of CNS. They may be suitable for persons with memory impairment linked with age, for rehabilitation after strokes, in learning disorders, posttraumatic stress disorders, neurodegenerative and mental disorders. It has been found that many transcription factors in the brain cortex are activated during vigilance and sleep deprivation, and are suppressed during sleep. Several-hour vigilance or sleep deprivation may trigger expression of many genes engaged in synaptic plastic-

ity and reaction to stress, and sleep may reverse this process. Non-invasive methods that can influence the synaptic plasticity include repetitive transcranial magnetic stimulation (rTMS) (22), which acts on pertaining cortical area, thus influencing the respective neuronal circuits. The method has been intensively and successfully studied within the treatment of depression, and the results indicate that this method could also have positive influence on cognition, independent on antidepressive effects.

CONCLUSIONS

Therapy of cognitive dysfunction seems to be a challenge for the 21st century. The significance of cognitive functions is more important in this era of immense technological progress than ever before. Psychiatry that has acquired sophisticated instruments, permitting the study of brain activity, becomes a perspective neuroscience branch. Psychiatry shares many problems with other branches, as the problem of cognitive dysfunction shows. However, the new fascinating findings, obtained by new brain-imaging techniques, molecular biology, genetics and pharmacogenetics, have been minimally used in clinical practice so far. An interdisciplinary approach may contribute to more rapid usage and verification of new experience, laying not only in cooperation but also in mutual respect.

Abbreviations

5-HT	- serotonin
ADHD	- attention-deficit/hyperactivity disorder
ACh	- acetylcholine
AMPA	- alpha-amino-hydroxy-methyl-(isoxazole) propionic acid
APs	- antipsychotics
COMT	- catechol-O-methyltransferase
CREB	- cAMP response element binding protein
MATRICES	- Measurement and Treatment Research to Improve Cognition in Schizophrenia
DA	- dopamine
NDRI	- noradrenaline and dopamine reuptake inhibitor
NMDA	- N-methyl-D-aspartate
NRI	- noradrenaline reuptake inhibitor
rTMS	- repetitive transcranial magnetic stimulation

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