

CORRELATIONS BETWEEN NEUROBIOLOGY AND PHARMACOTHERAPY OF CATATONIC STATES

Lidia NICA UDANGIU, Costin Emilian ROVENȚA

Lidia NICA UDANGIU – M.D., Ph. D, Professor, Dept. of Psychiatry, University of Medicine and Dentistry “Titu Maiorescu”, Bucharest, Romania; Senior Psychiatrist, Clinical Psychiatric Hospital “Al. Obregia” Bucharest, Romania

Costin Emilian ROVENȚA – M.D., Resident in psychiatry, Clinical Psychiatric Hospital “Al. Obregia” Bucharest, Romania

Abstract:

Catatonia occurs in a variety of psychiatric, medical and neurologic illnesses. Pathophysiology of catatonic states includes deficits in fetal cortical development, dopamine hypoactivity, dysfunction in neurotransmission of GABA, glutamate, noradrenaline and serotonin, frontal anomalies, or disorders of ion channels. The pathophysiology of catatonia has been linked to dysfunction of the prefrontal neocortical and paralimbic areas and associated circuits.

Keywords: catatonia, dopamine, GABA, glutamate

Introduction

Catatonia occurs in a variety of psychiatric, medical and neurologic illnesses. Etiologically, catatonia is most commonly identified in association with psychiatric disorders (mania, depression, schizophrenia and schizoaffective disorders, OCD-spectrum illness and dissociative disorders). Some hypotheses have been proposed about the pathophysiology of catatonic states:

- Deficits in fetal cortical development. The alterations in cerebral structure and function in schizophrenia suggest that an early disturbance of the central nervous sensory modality may be occurring in the patient and may contribute to the future development in schizophrenia and other developmental disorders. (1) These deficits are met in cortical and subcortical glutamatergic pathways, resulting in the symptoms and signs of catatonia.
- Desequilibrium in the excitatory/inhibitory ratio model: alterations in interrelated networks at the spinal and brainstem level may produce catatonia. (2)
- Dopamine (D) hypoactivity, specifically at the D₂ receptor is the main mechanism that leads to catatonia. The hypoactive D₂ receptor theory is confirmed by several case reports that demonstrate a relationship with high-potency typical antipsychotics either causing or worsening catatonia. This phenomenon is known as neuroleptic-induced catatonia. The decrease in activity at the D₂ receptor then causes an abundant release of glutamate, the major excitatory neurotransmitter. Glutamate is known to regulating the catecholamine release and is directly involved in dopamine regulation. (3) Glutamate has an excitotoxic effect, causing neuronal damage, and may produce symptoms similar to catatonia. (3,4)

- GABA, the major inhibitory neurotransmitter in the central nervous system, has an inverse relationship with glutamate. At high glutamate level, GABA acts to shut down glutamate release. Therefore, to further support the high glutamate activity and hypodopamine receptor theory, drugs that potentiate GABA (benzodiazepines) or act as GABA agonists (anticonvulsants) will have a benefit in treating catatonia. Modern neuroimaging techniques allow findings of cortical involvement in catatonia, but the main findings come from the pharmacology response to treatment. (3) Benzodiazepines are effective in 60% to 80% of patients with acute catatonia. (5) It has been described that 75% of patients can achieve sustained improvement with continuous treatment. (6) Also, Zolpidem, a non-benzodiazepine GABA-A agonist, is beneficial in catatonia. There are reports of cases of clinical durable improvement in patients with treatment resistance to ECT and benzodiazepines. These facts support GABA-A involvement in the pathophysiology of catatonia. (5) Moreover, GABA-A receptor binding in right lateral orbitofrontal and right posterior parietal cortex is diminished. There is also a report that correlates catatonic stupor with GABA-A binding decrease with flumazenil positron emission tomography scan. (6) This gabaergic binding normalized after the treatment with diazepam. (6) Another research performed with Spect with iodine-123-iomazenil showed lower cerebral perfusion in the right lower prefrontal cortex and parietal cortex in catatonic patients. In this group of patients the decrease of GABA-A receptor binding correlated positively with motor and affective symptoms. (7) Lorazepam and GABA-A agonists show that the principal dysfunction in catatonia may be related to GABA depletion. Potentiation of the action of GABA by benzodiazepines suggests that some individuals with catatonia may have a functional deficit of GABA. Benzodiazepine withdrawal can precipitate catatonia (8), and decreased benzodiazepine binding in the left sensorimotor cortex has been reported in catatonia. (7) The anticatatonic effects of benzodiazepines observed in treatment studies may be mediated by stimulation of gamma-aminobutyric acid GABA-A receptors. (9) Decreased binding to gamma-aminobutyric acid GABA-A receptors in the left sensorimotor cortex has been observed in some subjects with catatonia. The favourable responses of some patients with catatonia to benzodiazepines and zolpidem, agonists of GABA-A, suggest that this is a likely site of dysfunction, in some cases of catatonia.

- Glutamatergic dysfunction. The effectiveness of amantadine in the treatment of catatonia suggests that a part of patients manifest glutamatergic dysfunction. Glutamate transmission and N-methyl-D-aspartate (NMDA) antagonists may be involved in the pathophysiology of catatonia through NMDA receptors. For example, the NMDA (N-methyl-D-aspartate) receptor antagonists, ketamine and aptiganel (10) can induce psychosis and catatonia. It has been hypothesized that the decrease in gabaergic tone in prefrontal areas released the supplementary motor areas, resulting in glutamate disinhibition. Thus, the glutamatergic hyperfunction in the striatum may be related to the development of catatonic symptoms. (7) There are reports of successful treatments with glutamate antagonists: amantadine, topiramate, and memantine in patients who failed to respond to established treatment, including lorazepam and ECT. (11) With these compounds, clinical improvement seems to be gradual. This difference in the time response between GABA agonists and glutamatergic antagonists may suggest that glutamate hyperactivity may be a secondary reaction to gabaergic depletion. (11) When these findings are connected, catatonic syndromes are in part due to gabaergic hypoactivity and glutamate hyperactivity, and it seems that in this disorder it is necessary to have a balance between GABA and glutamate concentrations. When this balance is broken, catatonia may appear. According to current pharmacology, catatonia may be relieved by diminishing glutamate hyperactivity or by augmenting gabaergic tone.

- Dysfunction in neurotransmission of noradrenaline and serotonin:

- Animal models have been developed to study the pathophysiology of catatonia—Some findings suggest that dysfunction of dopaminergic, serotonergic, and glutamatergic systems may play a role in the production of catatonia in rats. Alekhina and colleagues reported decreases of noradrenaline and increases of serotonin in the striatum and diencephalon in rats with catalepsy. Noradrenergic dysregulation occurs in catatonia (12), and depletion of hypothalamic catecholamines was found in three patients dying of the malignant form. (13)

- Widespread loss of choline acetyltransferase — the biosynthetic enzyme for acetylcholine was also identified, but the role of acetylcholine in catatonia is much less clear.
- Frontal anomalies: Kahlbaum noted lesions of the Sylvian fossa and the second and third frontal gyri on autopsy of his patients who died with catatonia. (14) These regions modulate executive functions and the inhibition of voluntary acts.
- Finally, some cases of catatonia may result from a disorder of ion channels, given the discovery of a point mutation resulting in a conformational change in a brain-specific cation channel gene in several families with periodic catatonia. (15, 16)

The pathophysiology of catatonia has been linked to dysfunction of the prefrontal neocortical and paralimbic areas and associated circuits. For example:

- mutism is associated with damage to one (typically the left) supplementary motor area (involved in motor programming and in the initiation of voluntary and automatic movements) and/or the anterior cingulate gyrus (implicated in motivation) in the superomesial frontal region.
- generalized akinesia, waxy flexibility and catalepsy can be seen in bilateral lesions (17).
- in catatonic subjects (7) decreased cerebral blood flow has been reported in the right lower prefrontal (and parietal cortices).
- verbigeration, motor perseveration, mitgehen (“going with”) and gegenhalten (opposition to passive movements), automatic obedience are seen in both catatonia and frontal lobe disease.
- echolalia and echopraxia suggest the loss of frontal inhibitory control of the parietal lobe circuits mediating imitation behaviours.
- massive bilateral striatal lesions can also cause catatonia (17).
- as in parkinsonism, catatonic subjects show more difficulty with self-initiated movements than with externally provoked movements (18) again suggesting hypofunction of mesial frontal-striatal circuitry.
- prosectic speech is reminiscent of advanced Parkinson’s disease, with its attendant severe depletion of striatal dopamine.
- motor stereotypies could also reflect excessive dopaminergic activity in the dorsal striatum. The transition from catatonic excitement to mutism and akinesia might represent temporary exhaustion of presynaptic neuronal dopamine reserves, or more likely, the development of depolarization block (19) in postsynaptic striatal and hypothalamic neurons.
- psychomotor agitation in excited catatonia could reflect increased noradrenergic and dopaminergic activity in the nucleus accumbens, mediated via connections to the pedunculo-pontine nucleus, a cholinergic brainstem region involved in the programming and control of locomotion.
- a pathway from the amygdala, a subcortical nucleus in the temporal lobe that plays an important role in the experience of fear and anxiety. It may be important in the genesis of catatonic immobility and catalepsy arising during complex partial seizures and that associated with extreme emotional distress, such as observed during trauma situations.
- neuroimaging findings in catatonia are difficult to interpret, given the variability in reported results. Reductions in parietal (20), temporal (21) and frontal cortical activity have been variously reported (22).

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